

*current*

# DIAGNOSIS



# TREATMENT

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*Lange Medical Publications*

LOS ALTOS, CALIFORNIA



1963

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# *Preface*

This book is intended to serve the practicing physician as a useful desk reference on the most widely accepted technics currently available for diagnosis and treatment. It is not intended to be used as a textbook of medicine.

The wide acceptance of this book since its first appearance has been most gratifying. Annual revisions will be prepared for distribution in *January of each year*.

Although we have dealt primarily with internal medical disorders, discussions of other disorders commonly encountered in certain other specialties are included also.

As an aid to the physician in keeping informed on new drugs, a separate section on recently introduced drugs is now to be found in the appendix. Specific references to the clinical literature and general bibliographies have been added as a guide to further reading.

The authors have drawn freely from their own published works, and much excellent tabular and graphic material has been borrowed from other sources. Due acknowledgements are given at appropriate places in the text.

The editors wish to express their sincere thanks to their associate authors for participating so effectively in this venture. It is obvious that without their cooperation and assistance this book would not have been possible.

Henry Brainerd  
Sheldon Margen  
Milton J. Chatton

San Francisco, Calif  
January, 1963

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## General Symptoms

Milton J Chotton & Frederick H Meyers

### FEVER

The body temperature is normally subject to some individual variation as well as to fluctuation due to physiologic factors. Exercise, digestion, sudden increase in environmental temperature, and excitement (e.g., medical examination) may cause a transient increase in temperature. There is a slight sustained temperature rise following ovulation during the menstrual cycle and in the first trimester of pregnancy. The normal diurnal variation may be as much as  $2^{\circ}\text{F}$ , being lowest in the early morning and highest in the late afternoon.

Careful readings with a reliable thermometer, preferably inserted for 3-5 minutes, will prevent errors in clinical interpretation and possible serious error.

Methods of Determination & Normal Adult Values

Area	Average Temp	Range of Normal Temp
Rectal or vaginal	$99.6^{\circ}\text{F}$ ( $37.5^{\circ}\text{C}$ )	$98.5^{\circ}-99.8^{\circ}\text{F}$ ( $37.0^{\circ}-37.7^{\circ}\text{C}$ )
Oral	$98.6^{\circ}\text{F}$ ( $37.0^{\circ}\text{C}$ )	$96.7^{\circ}-99.0^{\circ}\text{F}$ ( $36.0^{\circ}-37.4^{\circ}\text{C}$ )
Axillary	$97.6^{\circ}\text{F}$ ( $36.5^{\circ}\text{C}$ )	$95.7^{\circ}-98.0^{\circ}\text{F}$ ( $35.4^{\circ}-36.7^{\circ}\text{C}$ )

#### Types of Fevers.

The characteristics of the temperature pattern (graphic record), especially when viewed in light of other clinical findings, may be of prognostic value and a guide to the effectiveness of therapy. The older classifications of fever according to type are of limited diagnostic significance but may be useful for descriptive purposes.

**A, Remittent:** Of days' or weeks' duration with alternating periods during which temperature is normal (e.g., brucellosis or tertian malaria). Temperatures should be taken 3-4 times daily for a prolonged period (weeks to

months) to demonstrate the alternating febrile and afebrile periods.

**B Intermittent** Temperature drops to normal or subnormal at least once in 24 hours (e.g., septic fevers and early tuberculosis). Temperature must be taken q.i.d. to demonstrate the variation within the day.

**C Unremittent or Continuous** Temperature never normal during 24-hour period (e.g., pneumonia, influenza). Temperature must be taken q.i.d. or, at times, every 2-3 hours to demonstrate its sustained character.

#### Diagnostic Considerations.

The outline below illustrates the wide variety of clinical disorders which may cause fever. Most febrile illnesses are easy to diagnose. In certain instances, however, the origin of the fever may remain obscure (FUO, PUO, or cryptogenic fever). Extensive laboratory and x-ray studies may be indicated, examination and culture of body fluids, exudates, and excretions, serologic tests, skin test, tissue biopsy, and toxicologic studies. Although fevers may be of psychogenic origin, this diagnosis should be made with extreme caution and should be based not only upon positive psychiatric criteria but after careful exclusion of the possibility of organic disease.

#### Clinical Classification of Causes of Fever (With Examples).

**A Infections** Viral, rickettsial, bacterial, fungal, and parasitic infections are the commonest causes of fever.

1 Generalized infections without localizing signs (e.g., septicemia).

2 Generalized infections with localizing signs (e.g., pharyngitis, scarlet fever).

3 Localized infections (e.g., pyelonephritis).

#### B Diseases of Undetermined Etiology

(1) Collagen diseases (e.g., disseminated lupus erythematosus, periarteritis nodosa,

## 2 Shock

dermatomyositis, rheumatoid arthritis, rheumatic fever) (2) Other miscellaneous diseases (e.g., sarcoidosis, amyloidosis)

**C. Central Nervous System Disease**  
Cerebrovascular accidents, head injuries, brain and spinal cord tumors, degenerative CNS disease (e.g., multiple sclerosis), spinal cord injuries.

**D Malignant Neoplastic Disease** Primary neoplasms (e.g., of thyroid, lung, liver, pancreas, and genitourinary tract) Secondary neoplasms, carcinoid

**E Hematologic Disease** Lymphomas, leukemias, multiple myeloma, pernicious anemia, hemolytic anemias, hemorrhagic diseases (e.g., hemophilia)

**F Cardiovascular Disease** Myocardial infarction, thromboembolic diseases, bacterial endocarditis, congestive heart failure, paroxysmal tachycardias

**G Endocrine Disease** Hyperthyroidism, pheochromocytoma

**H Diseases Due to Physical Agents** Heat stroke, radiation sickness, trauma (e.g., surgery), crushing injuries

**I Diseases Due to Chemical Agents**  
Drug reactions, anaphylactic reactions, serum sickness, chemical poisoning, pyrogen reactions (following I V fluids)

**J Disorders of Fluid Balance** Dehydration, acidosis

**K Psychogenic fever**

**L. Factitious fever**

### Treatment

**A Removal of the Specific Cause of the Fever** The principal problem is to determine and eradicate the cause of the fever. Symptomatic measures directed toward depression of an elevated body temperature are usually not indicated except for high, prolonged fevers

**B Reduction of the Fever by Nonspecific Means** When the body temperature is greater than  $40^{\circ}\text{C}$  ( $104^{\circ}\text{F}$ ), particularly if prolonged, the following measures may be utilized

1 Increased fluid intake - By oral or parenteral routes

2 Alcohol sponges - Cooling is due to evaporation

3 Warm or tepid baths - These cause peripheral vasodilatation.

4 Cold sponges - Provide prompt cooling of skin and psychologic relief but interfere with heat loss.

5 Ice bags - Provide local comfort, e.g., for headache

6 Antipyretic drugs - These drugs are quite effective in reducing fever and have a simultaneous analgesic effect. Their disadvantage is that they obscure the clinical picture, and may cause undesirable side effects such as sweating, nausea and vomiting, and, rarely, skin eruptions and hematologic changes. Such drugs, therefore, are to be employed cautiously in fevers due to infectious diseases and are preferably not used in the enteric fevers (e.g., typhoid fever). Acetylsalicylic acid (aspirin), 0.3-0.6 Gm. (5-10 gr.) every 4 hours p.r.n., is most commonly used. Other antipyretic analgesic drugs are listed on p. 6.

7. For reduction of very high fever [over  $41^{\circ}\text{F}$ . ( $105^{\circ}\text{F}$ .)], see Heat Stroke,

Bennett, I. L., Jr.: Pathogenesis of fever. *Bull. New York Acad. Med.* 37:440-4, 1961, Petersdorf, R. G., & P. Beeson: Favor of unexplained origin report on 100 cases. *Medicine* 40:1-30, 1961.

## SHOCK

(Circulatory Failure or Collapse)

Shock is a complex and as yet incompletely understood clinical syndrome of peripheral circulatory failure. Numerous pathophysiologic mechanisms are involved in the production of shock, such as lack of effective blood volume, alterations of cardiac output, loss of peripheral vascular tone, increased capillary permeability, and alteration of the physicochemical characteristics of the blood. Because such widely different mechanisms may result in the systemic arterial hypotension which is referred to as "shock," there is serious question concerning the desirability of retaining a catch-all term with such variable diagnostic and therapeutic meanings.

### Classification

The shock syndromes have been classified clinically according to etiology and pathophysiology as follows

**A Neurogenic Shock** (Primary, Immediate, or Psychogenic Shock, and Fainting or Syncope). This form of shock is usually vasovagal and caused by neurogenic or psychogenic factors, e.g., pain, trauma, fright, unpleasant

sights, sounds, or odors, or vasodilator drugs (e. g., nitrites, local anesthetics). Debility, asthenia, emotional instability, prolonged standing, excessive heat, alcohol, hypotensive drugs, and disorders of the autonomic nervous system predispose to neurogenic shock. The sudden autonomic overactivity results in vasodilatation or inhibition of constriction of the arterioles and rapid peripheral and splanchnic pooling of blood. Following a period of anxiety and signs of epinephrine release (tachycardia, tremors, and pallor), there is a sudden reflex vagal stimulation with decreased cardiac output, hypotension, and decreased cerebral blood flow. Although the patient usually recovers promptly in the recumbent position, observation is necessary to prevent recurrence and possible progression. (See Chapter 15 for a discussion of the various types of syncope.) If the condition persists, consider other and more significant underlying causes of shock.

**B Hypovolemic Shock (Secondary, Delayed Prolonged, Oligemic, Hemorrhagic, Traumatic, or Surgical Shock)** In this form of shock there is a true diminution of blood volume due to loss of whole blood or plasma from the circulation. Compensatory vasoconstriction reduces the size of the vascular bed and may temporarily maintain the BP, but if fluid is not replaced immediately hypotension occurs and the tissues become progressively more anoxic. Since the vascular space is the smallest of the body fluid compartments, even a moderate sudden loss of circulating fluids can result in severe and sometimes irreversible damage to vital centers. Rapid loss of 50% of blood volume is usually fatal.

Hypovolemic shock may result from (1) loss of whole blood by hemorrhage due to external or internal injuries, (2) loss of whole blood through nontraumatic internal hemorrhage (e. g., bleeding peptic ulcer, ruptured varices), (3) loss of blood and plasma in extensive fractures and crushing injuries, (4) loss of plasma and hemolysis of red cells in extensive burns, (5) loss of plasma into serous body cavities (e. g., peritonitis), (6) loss of plasma due to nephrotic syndrome, or (7) dehydration with electrolyte imbalance.

Debility, malnutrition, senility, hypotensive drugs (e. g., coronary vasodilators, "tranquilizers"), local anesthetics, general anesthetics, and adrenocortical insufficiency all predispose to hypovolemic shock.

The classical signs of pallor, coldness, cyanosis, sweating, tachycardia, and arterial hypotension may appear suddenly and often represent fully-developed shock. Since ad-

vanced shock is often refractory to even the most vigorous anti-shock therapy, early recognition or anticipation of shock is imperative.

**C. Shock Due to Infection (Septic, Endotoxic, or Exotoxic Shock)** The peripheral vascular collapse which follows the toxemia of overwhelming infection is characterized by an initial vasoconstriction followed by (or alternating with) vasodilatation, with venous pooling of blood. There is often a direct toxic action on the heart and adrenals. Shock should always be suspected when the febrile patient has chills, pallor, tachycardia, a moist skin, hypotension, and hyperpnea, especially if no other cause of shock is evident. Septic shock occurs more frequently in the very young and very old. It may be obscured by ineffective antibiotic therapy.

**D Cardiogenic Shock** Shock due to ineffective circulation associated with inadequacy of cardiac output may occur in myocardial infarction, severe tachycardia, and other serious cardiac arrhythmias, pulmonary embolism, cardiac tamponade, or terminal congestive failure.

**E, Allergic Shock. See Anaphylaxis**

**Treatment of Hypovolemic (Secondary) Shock**

**A Emergency Measures**

1 Place patient in the "shock position" (recumbent with head lower than the rest of the body) unless he has a head injury.

2 Maintain an adequate airway. If dyspnea or cyanosis is present, administer oxygen by nasal catheter or mask. Ensure adequate ventilation by mouth-to-mouth breathing. Pull out the tongue, remove dental plates from the mouth and mucus from the nose and mouth.

3 Keep the patient comfortably warm. Avoid chilling (to prevent heat loss), and excessive externally applied heat, which will further dilate the peripheral vessels.

4 Control pain (particularly if severe) promptly by the use of appropriate first aid measures and analgesic drugs. Give morphine sulfate, 10-30 mg ( $\frac{1}{16}$ - $\frac{1}{2}$  gr) subcut for pain, but remember that subcut absorption is poor in patients in shock. In case of severe pain, morphine sulfate, 10-15 mg ( $\frac{1}{16}$ - $\frac{1}{4}$  gr) I V, may be used to greatest advantage. Caution: Do not give morphine to unconscious patients, patients who have head injuries, those with respiratory depression, or those without pain.

#### 4 Shock

Avoid overdosage with morphine substitute barbiturates and salicylates for sedation and analgesia whenever possible

5 Allay apprehension by reassuring word and action Pentobarbital sodium (Nembutal®) 0.1 Gm (1½ gr) orally or 0.13 Gm (2 gr) subcut or by rectal suppository may be of value Avoid tranquilizing drugs because of their undesirable hypotensive effect

6 Parenteral fluid therapy - Replace and maintain adequate blood volume The need may be determined by the history vital signs hematocrit and when available blood volume studies The clinical determination of effective blood volume may be difficult and is subject to considerable variation There is no single technic or rule by which to judge the fluid requirements Response to therapy is a valuable index Selection of the replacement fluid which is most appropriate to the individual case is based upon consideration of what type of fluid has been lost (see pathophysiology above) the availability of the various solutions laboratory facilities and to a lesser extent expense

(1) Saline or glucose solutions - Give immediately 500 ml sodium chloride injection or 5-10% dextrose injection or 200 ml of 5% saline solution (may be given rapidly I V while making preparations for plasma serum albumin or whole blood) Plasma serum albumin and whole blood exert a more sustained increase in blood volume through the colloidal osmotic pressure effect than do dextrose or electrolyte solutions

(2) Whole blood - Whole blood may sometimes be of value in the treatment of severe or refractory shock even in the face of an apparently good hematocrit figure this is because of the misleading effect of hemoconcentration (a) For impending shock administer 250-500 ml of blood immediately and follow closely clinically and with hematocrit and blood volume studies to determine need for further plasma (b) For early or advanced shock administer 500 ml whole blood immediately and repeat with 500 ml every half hour up to a total of 2 L, depending upon the presence of continued hemorrhage, clinical course and hematocrit and blood volume findings If shock persists, the prognosis is very poor

(3) Plasma or serum albumin - Any of the various plasma preparations such as lyophilized or reconstituted plasma may be employed Plasma is usually readily procurable may be rapidly set up for administration and does not require preliminary blood typing The quantity of plasma to be given depends upon the stage of shock and the response to therapy, based upon both clinical and laboratory studies

(4) Plasma expanders - Fairly effective plasma substitutes for emergency treatment of shock are now available These agents have high molecular weights, high oncotic pressures, and the necessary viscosity, but they have not proved to be as useful as plasma They have the added advantage of not causing infectious hepatitis Dextran injection (Expandex®, Gentran®, Plaviolex®) is a water-soluble biosynthetic polysaccharide available as a solution in isotonic saline for I V use Give 500-1000 ml at a rate of 20-40 ml/minute Use cautiously in patients with cardiac or renal insufficiency Anaphylactoid reactions have been reported In order to avoid hemodilution the dosage should not exceed that which maintains the systolic BP at about 85 mm Hg

7 Vasopressor drugs - These agents are most effective in hypotensive shock without associated decrease in blood volume (e.g., spinal anesthesia myocardial infarction, and overwhelming intoxications), although they are of at least transient value in severe shock due to any cause They should not be used in lieu of more physiologic measures or specific treatment of the cause of shock In many instances it is doubtful whether the BP elevation produced by the vasopressor drugs has either a beneficial or detrimental effect upon the underlying disturbance (For example, the actual influence of the altered peripheral resistance on the blood supply to vital organs is incompletely understood) Dosage levels for the various agents are empiric and must be carefully adjusted according to patient response (BP and pulse)

(1) Levarterenol bitartrate (Levophed®) 4-16 mg (4-16 ml of 0.2% solution) in 1 L of glucose I V Avoid extravasation (may cause tissue necrosis and gangrene) Constant supervision with regular determination of BP is essential With concentrations greater than 4 mg/L, an indwelling catheter is required

(2) Phenylephrine hydrochloride (Neo-Synephrine®) 0.5 mg I V, or 5 mg I M or by slow I V infusions of 100-150 mg/L of glucose

(3) Mephentermine sulfate injection (Wyamine®) 5-20 mg at a rate of 1 mg/minute by continuous I V infusion of a 0.1% solution in 5% dextrose in water or 15-20 mg I M

(4) Metaraminol bitartrate (Aramine®) 2-10 mg I M or 15-100 mg in 250-500 ml of 5% dextrose or 0.5-5 mg I V

(5) Methoxamine hydrochloride (Vasoxyl®) 15 mg I M or 5 mg I V, or 35-40 mg in 250-500 ml of 5% dextrose by slow I V infusion



### B. Specific Measures

1. Hemorrhage and anemia - Although plasma is usually given as an emergency measure in shock complicating hemorrhage, acute anemia must be corrected by replacement with whole blood to prevent hypoxia. The quantity of whole blood to be given will depend upon clinical response, hematocrit, and, when available, blood volume studies.

2. Anoxia (or hypoxia) - Oxygen may be indicated for hypoxia due to disorders such as cardiac failure and pneumonia. However, the patient in impending shock is apprehensive, and the mask or tent may increase his apprehension.

3. Dehydration - Administer 500-1000 ml of sodium chloride injection or 5% dextrose injection, I.V. or by hypodermoclysis as needed. As soon as the patient can swallow, give fluids by mouth. Unless there is specific clinical or biochemical evidence of sodium deficiency, avoid administration of more than 1 L. of saline solution on the first day. Subsequent parenteral fluids may be given as dextrose solutions (see Chapter 2).

4. Adrenocortical failure - Adrenocortical steroid therapy has been found to be effective in shock-like states associated with serious medical emergencies. Although steroid treatment is most specifically applicable to shock of Addison's crisis, it may also be of spectacular value in certain acute allergic emergencies and overwhelming intoxications. Give hydrocortisone sodium succinate (Solu-Cortef®) (or equivalent), 100-300 mg as a 5% solution in sterile water or isotonic saline solution, rapidly I.V. Subsequent doses of 50 mg. may be given as required. Doses of 500-1000 mg. daily for 3-5 days may be necessary.

5. Cardiac failure - Digitalis and other drugs for treatment of cardiac failure are indicated only for those patients with pre-existing or presenting evidence of cardiac failure. Use parenteral fluids cautiously and avoid sodium-containing solutions. Digitalis is of no value in shock due to any other cause.

6. Infection - Immediate measures should be taken to combat infection, if present. Early recognition is important. Initiate bacteriologic studies immediately and before therapy, if possible. Overwhelming infections are capable of producing sufficient metabolic changes in the body tissues to predispose to shock. Institute preliminary broad-spectrum antibiotic therapy until bacteriologic studies reveal the identity of the organism. "Prophylactic" antibiotics are of doubtful value and may even be harmful, except when the hazard of infection is great (e.g., extensive burns). Give hydrocortisone

or its equivalent in doses of 250-500 mg I.V. every 8-12 hours for 3 days, and supportive measures such as oxygen, pressor drugs, and parenteral fluids.

C. Evaluation of Therapy - Constant observation of patient is imperative. The pulse, respiration, temperature (rectal), and BP should be taken immediately and every 15-30 minutes or oftener thereafter until peripheral circulation has definitely improved.

1. Rapid recovery - If vital signs return rapidly to normal, keep the patient under close observation but withhold further anti-shock therapy. Check vital signs every half-hour. Determine hematocrit if there is any suspicion whatever that shock persists. Remember that hemoconcentration usually precedes BP and pulse changes. After eliminating potential or existing shock-producing factors, the patient may be managed expectantly until it is reasonably certain that the danger has passed.

2. Delayed recovery - If the vital signs remain abnormal for even a brief period after initial measures have been taken, or if there is evidence of progression of peripheral circulatory failure, institute further vigorous antishock therapy. Blood hemoglobin, RBC, and hematocrit should be determined immediately for a base-line, and should be repeated as often as necessary to evaluate the results of therapy.

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## PAIN

Pain is usually sharply localized in disorders of superficial structures and peripheral (spinal or cranial) nerves, and diffuse or poorly localized in disorders of deeper structures. Deep pain may be "referred" to other areas of the body (e.g., shoulder pain in gall-bladder disease). The reaction to pain as a function of the higher centers, is extremely variable and influenced by many factors.

It is important to determine whenever possible the primary etiology (e.g., infection, toxins) and the pathogenesis (e.g., inflammation, ulceration, distention, anoxia, spasm) of pain. In most disorders it is possible to determine both the etiology and pathogenesis of pain (e.g., pleurisy associated with pneumococcal pneumonia), in other instances it is not possible to determine either (e.g., trigeminal neuralgia).

The relief of pain is achieved by removal of the primary cause (e.g., cure of infection), neutralization of the effect of the stimulus (e.g., antacids for hyperacidity of peptic ulcer) and, when these are not feasible, by dulling or obliteration of the sense of pain (e.g., palliative narcotics for terminal cancer). The psychic relief of pain by hypnosis has been popularized as a means of analgesia in a wide variety of disorders. It is essential that hypnosis be administered by a professional person who has received special training in this field.

The hazards of administering analgesics without first attempting to establish a diagnosis cannot be overemphasized (e.g., acute abdominal pain). Analgesics, particularly narcotics, may mask the symptoms of serious acute or chronic illness.

Pain may be treated nonspecifically with drugs, physical measures (e.g., heat, cold, immobilization), or surgery (e.g., nerve resection, chordotomy). Narcotic analgesics should be avoided unless nonnarcotic drugs (in adequate dosage) would be ineffective. When narcotics are required the relatively less addictive drugs (e.g., codeine) should be employed first. One should prescribe the lowest effective dosage of narcotics and discontinue as soon as possible.

Because psychic or emotional factors may greatly influence the pain threshold, it is important to consider the "placebo" role of all therapeutic measures for the control of pain. Pharmacologically inactive drugs may be surprisingly effective in alleviating the pain of organic as well as functional disorders.

## Nonnarcotic Analgesics

**A Salicylates** The salicylate drugs are antipyretic, analgesic, antirheumatic, and uricosuric, useful in relieving myalgias, neuralgias, arthralgias, headaches, and dysmenorrhea. Untoward reactions are usually mild, consisting of dizziness and dyspepsia, but large doses may cause tinnitus, deafness, blurring of vision, nausea and vomiting, diarrhea, diaphoresis, headache, and delirium. In sensitive patients, salicylates may cause urticarias and acute laryngeal edema.

**1 Acetylsalicylic acid (aspirin or ASA), plain, buffered, or enteric-coated, 0.3 Gm (5 gr.) tablets.** Ordinary dosage is 0.3-0.6 Gm (5-10 gr.) every 4 hours p.r.n., 0.3 Gm (5 gr.) every 2-3 hours is said to be more effective and to cause fewer untoward reactions. The plain preparation may cause gastric distress, this may be avoided by administration of the drug on a full stomach or with 1/2-1 tsp. of baking soda or other antacid, or by the use of buffered aspirin tablets. The buffered aspirin usually available contains only small amounts of antacid, and the incidence of side effects and the blood levels achieved are not appreciably different than with ordinary aspirin. The enteric preparation is slower acting, but it prevents gastric irritation and is also useful for those patients who might be skeptical of the analgesic value of "ordinary aspirin." In certain cases it may be necessary to administer powdered aspirin rectally in a thin starch paste.

**2 Sodium salicylate, plain or enteric-coated, 0.3-0.6 Gm. (5-10 gr.) every 4 hours p.r.n.**

**3. Acetylsalicylic acid compound (APC) contains aspirin, phenacetin, and caffeine.** It is given as 1-2 tablets every 3-4 hours p.r.n. No advantage of this combination over ordinary aspirin has been conclusively demonstrated. The amounts of phenacetin ingested by habitual users of this combination are reported to cause serious renal damage.

**4 Methyl salicylate (wintergreen oil) -** For external use as a 10% oil or ointment applied over sore muscles or joints.

**B. Acetophenetidin (phenacetin), 0.3 Gm (5 gr.) every 3-4 hours,** may be employed in case of salicylate intolerance. In general, however, this drug is more toxic than other nonnarcotic analgesic preparations, and prolonged use is not advised. Its principal use is in analgesic combinations (e.g., APC).

**C. Colchicine -** See Gouty Arthritis

**D. Phenylbutazone (Butazolidin<sup>®</sup>) or Oxyprenbutazone (Tandearil<sup>®</sup>)** See Gouty Arthritis

**E Dextro Propoxyphene (Darvon®) and Ethoheptazine (Zactane®)** Although related chemically to other narcotics, these drugs are less potent in all respects. Side effects are uncommon (dizziness, epigastric pain, nausea) and addiction is not a problem, but the claim that these drugs are comparable to codeine has been disproved. They are usually dispensed in combination with aspirin compound (Darvon Compound®, Zactin®) every 4-6 hours p. r. n. No narcotic prescription is required.

### Narcotic Analgesics

The narcotic analgesics alter the perception of pain by their effects on the CNS. They are indicated for the relief of pain which is too intense to be controlled with nonnarcotic drugs or when pain is of a type not relieved by the salicylates (e.g., visceral pain).

The narcotics are also mildly sedative in small doses, larger doses produce sleep, stupor, and respiratory depression. They are addictive and should be used cautiously and with careful attention to federal and state laws. Except for codeine, they should not be used for chronic illnesses except when necessary for the control of otherwise intractable pain in terminal illness.

Addiction is discussed in Chapter 16.

The specific treatment of intoxication with these drugs is discussed in Chapter 28.

The standard drugs and their congeners are discussed below.

**Note.** Always use the least potent narcotic drug which will control the pain, i.e., aspirin is preferable to codeine, codeine to meperidine, and meperidine to morphine.

**A Morphine** This drug is the most valuable of the potent narcotics for general clinical use. It causes CNS depression which results in powerful analgesia associated with sedation, euphoria, and hypnosis, selective respiratory center depression, and dulling or abolition of the cough reflex. It increases intracranial pressure and causes spasm of biliary and ureteral smooth muscle. Morphine is useful for relief of acute or prolonged severe pain, especially pain arising from disorders which are of less than 10-14 days' duration. The drug may be valuable in the treatment of severe cardiac dyspnea (e.g., pulmonary edema or cardiac asthma of "left ventricular failure"). It is a commonly used and valuable preoperative drug. Morphine is contraindicated in morphine sensitivity, bronchial asthma, undiagnosed surgical abdominal disease, liver disease, hypothyroidism, morphinism, head injury, Addison's disease, and whenever vomiting may be dangerous. Untoward

reactions include hypnosis (may be undesirable), respiratory depression, nausea and vomiting, severe constipation, allergic responses (urticaria, pruritus, and anaphylactoid reactions). The addiction tendency is great.

**1 Morphine sulfate, 8-15 mg (1/8-1/4 gr)** orally or subcut in cases of severe agonizing pain, especially pain associated with impending neurogenic shock (e.g., acute pancreatitis), it may be given slowly in 5 ml physiologic saline I.V. It is probable that only increased duration of effect is gained by increasing the dose above 10 mg.

**2 Morphine adjuncts - Belladonna alkaloids** such as atropine and scopolamine, in dosages of 0.3-0.6 mg (1/200-1/100 gr) subcut administered simultaneously with morphine may reduce some of the untoward effects of morphine. Scopolamine may enhance the analgesic effect.

**B Morphine Congeners** A number of drugs equivalent to morphine but offering no advantages are available. Claims of fewer side effects should be regarded with skepticism.

The following subcut doses are equivalent to 10 mg of morphine: dihydromorphine (Dilaudid®), 2 mg; levorphanol (Levo-Dromoran®), 2 mg; oxymorphone (Numorphan®), 1 mg; phenazocine (Prinadof®), 1 mg; piminodine (Alvodine®), 7.5 mg.

**C Methadon (Dolophine®)** Methadon, 5-10 mg subcut, provides analgesia similar to that achieved with morphine. The onset is slower and the effect is more prolonged. It has powerful addictive properties. The only situation in which methadon is preferred is in the institutional treatment of addiction, withdrawal symptoms are ameliorated if methadon is first substituted for heroin or whatever opiate the addict has been taking.

**D Meperidine (Demerol®)** 50-100 mg orally or 1 M (not subcut) every 3-4 hours provides analgesia and causes less intense side effects than morphine. It is also less addictive than morphine, but addiction to meperidine is nevertheless very common.

**E Meperidine Congeners** Alphaprodine (Nisental®), 60 mg subcut, and antleridine (Leritine®) 50 mg subcut, are equivalent to meperidine, 100 mg, except that their duration of action is shorter.

**F Dihydrocodeinone and Dihydrohydroxycodeinone** These narcotics are present in

## 8 Allergic Disorders

many combinations and are frequently misused because the names suggest a similarity to codeine. Both are more potent and more addictive than codeine.

**G Codeine** Codeine is pharmacologically similar to morphine but is less potent. CNS depression occurs in ordinary dosages. Codeine diminishes the cough reflex and decreases bowel motility (constipating). It is preferred to morphine for relief of moderate degrees of pain because it is much less habit forming and causes fewer untoward reactions (urticaria, nausea and vomiting, pruritus, dermatitis, anaphylactoid reactions).

1 Codeine phosphate 8-65 mg ( $\frac{1}{8}$ -1 gr) orally or subcut every 3-4 hours p r n. If 65 mg (1 gr) is ineffective, use stronger narcotics, since larger doses of codeine are attended by increasing side reactions without increasing analgesia.

2 Codeine in dosages ranging from 8-65 mg ( $\frac{1}{8}$ -1 gr) is often used in combination with acetylsalicylic acid or ASA compound. The dosage is one tablet orally 3-4 times daily as necessary. In such mixtures codeine is the active ingredient; the aspirin is added for convenience in prescribing.

## ALLERGIC DISORDERS

Allergic disorders may be manifested by generalized systemic reactions or by localized reactions in any organ system of the body. The reactions may be acute, subacute, or chronic and may be caused by an endless variety of offending agents (antigens). Many of the obscure or so-called idiopathic disorders are considered to have a possible allergic origin.

### Allergic Reactions in Nonallergic ("Normal") Individuals

Development of sensitization through contact with the antigen is more or less apparent. These reactions occur in a large percentage of "normal" individuals without evident hereditary predisposition. The diagnosis may be readily confirmed by appropriate skin testing or therapeutic trial (caution).

- 1 Serum sickness
- 2 Drug anaphylaxis
- 3 Dermatitis venenata
- 4 Tuberculous sensitization

### Atopic Disorders

These "natural or spontaneous" allergies occur in about 10% of the population, often with a family history of the same or a similar disorder. Antigenic etiology is much more obscure than in the case of the "normal" allergies. Determination of the allergens is much more difficult since complete reliance cannot be placed upon clinical history, skin tests, or elimination diets. Eosinophilia is characteristic but not pathognomonic of atopic disorders.

- 1 Hay fever (allergic rhinitis)
- 2 Eczema
- 3 Urticaria
- 4 Angioneurotic edema
- 5 Allergic purpura
- 6 Allergic migraine
- 7 Allergic asthma
- 8 Anaphylactic reactions

### Anaphylactic Reactions (Anaphylactic Shock)

Anaphylactic reactions are the immediate shock-like and frequently fatal reactions which occur within minutes after administration of foreign sera or drugs. Although there is occasionally no history of previous exposure to the foreign substance, these acute reactions undoubtedly represent induced hypersensitivity. Anaphylactic reactions may occur following the injection of sera, penicillin and other antibiotics, and practically all repeatedly administered parenteral therapeutic agents. Note: For this reason, sensitizing drugs should not be administered indiscriminately by oral, topical, or parenteral routes. Emergency drugs should be available whenever injections are given.

Symptoms of anaphylaxis include apprehension, paresthesias, generalized urticaria or edema, choking sensation, cyanosis, wheezing, cough, incontinence, shock, fever, dilatation of pupils, loss of consciousness, and convulsions; death may occur within 5-10 minutes.

#### A Emergency Treatment

- 1 Epinephrine solution, 1 ml of 1:1000 solution (1 mg) I M stat., repeated in 5-10 minutes and later p r n. If the patient does not respond immediately, give 0.1-0.4 ml of 1:1000 solution diluted in 10 ml saline slowly I V.
- 2 Place in shock position. Keep warm.
- 3 Maintain adequate airway.
- 4 Diphenhydramine hydrochloride (Benadryl<sup>®</sup>), aqueous, 5-20 mg I V, after epinephrine if necessary.
- 5 Hydrocortisone sodium succinate (Solu-Cortef<sup>®</sup>), 100-250 mg, or prednisolone hemisuccinate (Metacortelone<sup>®</sup>), 50-100 mg in

water or saline I V over a period of 30 seconds, after epinephrine or diphenhydramine for prolonged reactions

6 Positive pressure oxygen therapy (see Chapter 7)

7 Aminophylline injection, 250-500 mg in 10-20 ml of saline slowly I V, may be of value

## B Prevention

1 Precautions - Be aware of the danger Do not use potentially dangerous drugs unless there is a definite need Avoid giving drugs to patients with a history of hay fever, asthma, or other allergic disorders unless necessary Whenever possible, determine by inquiry whether the patient has been given other injections of the drug he is about to receive If he reports any allergic reaction on prior administration, do not give the injection

2 Prior administration of antihistaminic drugs (for selected patients) - Reduction of frequency and severity of anaphylactic reactions by means of the antihistaminic drugs has been reported The antihistamines, however, do not guarantee safety against anaphylaxis in certain hypersensitive individuals

3 Cautious administration of corticotropin 1-2 hours before drug injection has been suggested, but clinical experience is limited and at best difficult to evaluate.

4, Desensitization - See Chapter 20

## Serum Sickness.

Serum sickness is a systemic allergic reaction which occurs within 1-2 weeks after injection of any foreign serum (e.g., tetanus or diphtheria antitoxin). It is characterized by malaise, fever, urticaria, patchy or generalized rash, lymphadenopathy, musculoskeletal aches and pains, nausea and vomiting, and abdominal pain. It is usually mild and lasts about 2-3 days. Serious neurologic complications occur very rarely. In previously sensitized individuals the reaction may be severe or even fatal, and the onset may occur immediately after the injection or after a latent period of several hours to a few days.

## A. Prevention

1. Recognition of individual hypersensitivity is based upon a history of allergic diathesis or previous drug or serum reactions and warrants special preliminary testing for sensitivity and careful precautions in administering immunizing sera.

2. Testing for serum sensitivity - See p. 666.

3. Desensitization - If there is any evidence of sensitivity by either the conjunctival

or intradermal sensitivity testing technics, it is imperative that the patient be desensitized with graded doses of the serum to be employed (see p. 666).

## B. Treatment.

1. Mild reactions - Antihistamines [e.g., tripelemnamine (Pyribenzamine<sup>®</sup>) or diphenhydramine (Benadryl<sup>®</sup>)], 25-50 mg. every 4 hours p.r.n., or salicylates p.r.n.

2. Moderate or prolonged reactions - Antihistamines, epinephrine, ephedrine, or the corticosteroids may be required.

3. Severe reactions - See Anaphylactic Reactions, p. 8.

## Drugs Used in Allergic Disorders.

Many manifestations of allergic reactions are due to the liberation of histamine from storage sites in the body The treatment of allergies may thus consist of administering drugs which (1) prevent the effects of histamine (antihistaminic drugs), (2) reverse the effects of histamine (epinephrine, ephedrine, and related sympathomimetic drugs) or (3) suppress the allergic inflammatory reaction (steroids)

A The Antihistamines The antihistaminic drugs do not prevent the release of histamine caused by the antigen-antibody reaction but they do, to a limited extent, prevent the histamine from acting on blood vessels, bronchioles, and other end organs

The antihistamines are most effective in urticaria, angioneurotic edema, hay fever, and serum sickness They are less predictably useful in vasomotor rhinitis and contact dermatitis, and are least apt to be effective in atopic dermatitis

The most common side effect is sedation of the type produced by the tranquilizers, this effect may be useful, but is often regarded as unpleasant by the patient Other side effects are feelings of weakness, various gastrointestinal complaints, and atropine-like effects such as dry mouth or blurred vision Larger doses cause excitement, i.e., insomnia and tremulousness progressing to confusion and convulsions

The antihistamines should not be used topically since they are common sensitizers and are not locally effective

In a given patient the choice of preparation depends upon trial and error and a decision about whether sedation is desired or not

Some commonly used antihistaminic drugs and their usual dosages are as follows

- 1 Sedation infrequent -
  - \*Chlorpheniramine (Chlor-Trimeton<sup>®</sup>, Teldrin<sup>®</sup>), 4 mg q i d
  - \*Brompheniramine parabromdylamine (Dimetane<sup>®</sup>) 4 mg q i d
  - \*Dexchlorpheniramine (Polaramine<sup>®</sup>) 2 mg q i d
  - Dexbrompheniramine (Disomer<sup>®</sup>), 2 mg q i d
  - Carbinoxamine (Clistin<sup>®</sup>), 4 mg q i d
- 2 Sedation often prominent -
  - \*Diphenhydramine (Benadryl<sup>®</sup>) 50 mg q i d
  - Bromodiphenhydramine (Ambodryl<sup>®</sup>) 25 mg q i d
  - \*Tripropylamine (Pyribenzamine<sup>®</sup>) 25 mg q i d
  - Pyrilamine (Neo-Antergan<sup>®</sup> contained in many combinations and brands) 50 mg q i d
  - \*Promethazine (Phenergan<sup>®</sup>), 12.5-25 mg b i d Give b i d only About twice as expensive as others
  - Doxylamine (Decapryn<sup>®</sup>) 25 mg b i d
  - Methapyrilene (Seminon<sup>®</sup>, Histadyl<sup>®</sup> Therylene<sup>®</sup>) 50-100 mg q i d (Used in proprietary "sleeping tablets")
  - Clemizol (Allercur<sup>®</sup>, Reactrol<sup>®</sup>) 40 mg q i d
  - Diphenylpyraline (Dlafen<sup>®</sup>, Hisapril<sup>®</sup>), 2 mg q i d (A diphenhydramine congener)
  - Methdilazine (Tacaryl<sup>®</sup>), 8 mg b i d (A phenothiazine)
  - Pyralthiazine (Pyrrolazote<sup>®</sup>), 25 mg q i d (A phenothiazine)
  - Thonzylamine (Anahist<sup>®</sup>, Neohetramine<sup>®</sup>) 50-100 mg q i d

Cyproheptadine (Periactin<sup>®</sup>), 4 mg q i d

- 3 Other long-acting antihistamines -
  - Chlorcyclizine (Di-Paralene<sup>®</sup>, Perazil<sup>®</sup>) 50 mg b i d
  - Triprolidine (Actidil<sup>®</sup>), 2-5 mg b i d
  - Pyrrbutamine (Pyronit<sup>®</sup>) 15 mg b i d

**B Sympathomimetic Drugs** The sympathomimetic drugs have actions opposite to those of histamine. The antihistamines may prevent further histamine effects; the sympathomimetics can counteract changes that have already occurred. Therefore, in emergency situations epinephrine is the drug of choice (see Anaphylaxis above). In chronic situations ephedrine is useful either by itself or to supplement the effects of the antihistamines. (For dosages and other information about ephedrine and epinephrine see Bronchial Asthma.)

**C Anti-inflammatory Steroids** In some acute allergic reactions (e.g. poison ivy dermatitis, drug and serum reactions, and in chronic allergies in which the severity justifies the use of an agent with diverse and profound effects, corticosteroids are very effective. (For dosages and other information about these drugs, see Bronchial Asthma and the discussions in Chapters 4 and 17.)

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# Fluid & Electrolyte Disorders

Frank A. Gotch & Isidore S. Edelman

Normally, the body fluids have a specific chemical composition and are distributed in discrete anatomic compartments of relatively fixed volumes. Disease produces associated or independent abnormalities in concentration, distribution, and amounts of the body fluids. Correct diagnosis and treatment of fluid and electrolyte disorders depends upon an understanding of the chemical laws and physiologic processes which control these 3 features of the body fluids.

## BASIC CONSIDERATIONS\*

### ELECTROLYTE CHEMISTRY

An electrolyte is any compound capable of conducting an electric current. It is composed of positively and negatively charged atoms or molecules called ions, which are held together by means of electron transfer (ionic bonding). An atom or molecule which donates electrons becomes a positively charged particle (cation), the atom or molecule which accepts these electrons becomes a negatively charged particle (anion). For each electron transferred, one positive charge is left on the cation and one negative charge is produced on the anion. In any electrolyte or electrolyte solution the total of the cation charges must equal the total of the anion charges. This is the law of electroneutrality of solutions.

The number of electrons an atom or molecule donates or accepts is called its valence. Valence determines the number of cations and anions which will be combined in each molecule of the electrolyte.

When electrolytes are put into solution, the cations and anions separate (dissociate) and form discrete, charged particles. In solutions of strong electrolytes virtually all the cations and anions will separate, in solutions

of weak electrolytes only some of the ions dissociate. In body fluids the strong electrolyte ions are  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ , and  $\text{SO}_4^{2-}$ . The weak electrolytes are the acids  $\text{H}_2\text{CO}_3$ ,  $\text{H}^+$ , Protein,  $\text{H}^+$  Hemoglobin,  $\text{H}_2\text{PO}_4^-$ , and the organic acids.

A mol (gram-molecule) is the molecular weight of a substance expressed in grams. An equivalent is the molecular weight in grams of a substance divided by its valence, i.e.,

$$\text{One Eq} = \frac{\text{mol wt}}{\text{valence}}$$

For substances with a valence of 1, therefore, one mol is equal to one equivalent, and for substances with a valence of 2, the equivalent weight will be one-half the molecular weight, e.g., 1 Eq  $\text{Na}^+$  or  $\text{Cl}^-$  = mol wt  $\text{Na}^+$  or  $\text{Cl}^-$  — 1, 1 Eq  $\text{SO}_4^{2-}$  = mol wt  $\text{SO}_4^{2-}$  — 2. Equivalents denote combining power, i.e., the ability of anions and cations to join with each other. Since in any solution the number of positive charges must equal the number of negative charges (law of electroneutrality), 1 mol of  $\text{Na}^+$  will combine with 1 mol of  $\text{Cl}^-$ , but 2 mols of  $\text{Na}^+$  will combine with 1 mol of  $\text{SO}_4^{2-}$ . Because ions are present in the body in minute quantities, they are measured in milliequivalents (mEq,  $\frac{1}{1000}$  Eq) and millimols (mM,  $\frac{1}{1000}$  mol).

The following relationships are useful for the conversion of the quantities discussed above:

To convert grams into mM:

$$\text{mM} = \frac{\text{Gm.} \times 1000}{\text{mol. wt}} = \frac{\text{mg}}{\text{mol wt}}$$

To convert grams into mEq

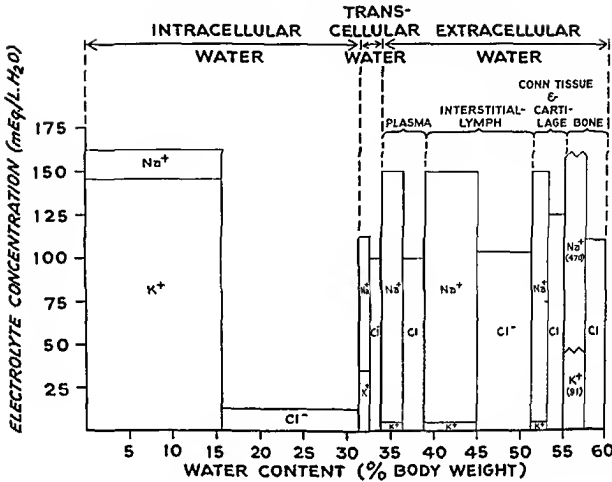
$$\text{mEq.} = \frac{\text{Gm} \times 1000 \times \text{valence}}{\text{mol wt}} = \frac{\text{mg} / 100 \text{ ml} \times 10 \times \text{valence}}{\text{mol. wt.}}$$

To convert mg / 100 ml into mM./L.

$$\text{mM} / \text{L} = \frac{\text{mg.} / 100 \text{ ml.} \times 10}{\text{mol. wt.}}$$

\*The discussion of clinical problems begins on p. 26

Distribution of Water & Electrolytes in Average Adult Male



Concentrations of Cations & Anions Present in Plasma, ISW, & ICW

	Plasma		ISW, mEq /L *	ICW, mEq /L
	Average	Range		
Na <sup>+</sup>	140	138-145	144	10
K <sup>+</sup>	4	3.5-4.5	4	150
Ca <sup>++</sup>	5	4.8-5.65	5	
Mg <sup>++</sup>	2	1.8-2.3	2	38
Total <sup>+</sup>	151		*	198
Cl <sup>-</sup>	103	97-105	117	3
HCO <sub>3</sub> <sup>-</sup>	27	26-30	30	10
Protein <sup>-</sup>	16	14-18		65
HPO <sub>4</sub> <sup>-</sup>	2	1.2-2.3	2.3	100
SO <sub>4</sub> <sup>-</sup>	1		1.1	20
Undetermined anions <sup>-</sup>	2		2.3	
Total <sup>-</sup>	151		*	198

\*Concentrations derived by converting plasma concentrations to mEq / L of serum water and applying Donnan factors of 0.95 for cations and 1.05 for anions



To convert mM /L into mEq /L

$$\text{mEq /L} = \frac{\text{mM} \times \text{valence}}{\text{L}}$$

$$\frac{\text{mg / 100 ml} \times 10 \times \text{valence}}{\text{mol wt}}$$

## OSMOSIS & OSMOTIC PROPERTIES OF SOLUTIONS

Almost all cell membranes in the body are similar to semipermeable membranes insofar as they permit a free flow of water but restrict the flow of various solutes. The selective flow of water across a membrane which is poorly permeable to solute molecules has been termed osmosis. The most widely accepted explanation of this process is that the membrane contains pores of the proper size to allow free movement of water molecules through the membrane while solute molecules are too large to pass through the pores. Consequently there is continuous movement or flux of water molecules back and forth across the membrane due to the kinetic energy of these molecules.

If a semipermeable membrane separates one portion of pure water from another portion of pure water, there will be no net transfer of water across the membrane since the same number of water molecules will strike the membrane on each side (since the kinetic energy of the water on both sides of the membrane is equal). If one or more solutes to which the membrane is impermeable are added on one side, there will be net movement of water to that side because the presence of the solute molecules will permit fewer water molecules to have access to the pore openings on the solution side relative to the pure water side of the membrane. Since the net movement of water is determined by the number of solute molecules present, it follows that a net flow of water will also take place if there is a different concentration of solute molecules on the 2 sides of the membrane (an osmotic gradient). If no force is applied to prevent this flow, water transfer will continue until solute concentration is equal on both sides of the membrane, the osmotic gradient is dissipated and osmotic equilibrium restored.

Osmotic pressure is defined as the force per unit area applied to the side of the semipermeable membrane with the higher concentration of solute molecules just sufficient to prevent net water movement to that side. Since the osmotic pressure of a solution is

directly proportional to the concentration of discrete molecular particles it contains, it can be expressed in terms of the concentration of solute molecules present. One convention for expressing the effective osmotic concentration is osmola/L or milliosmols/L (mOsm  $\frac{1}{1000}$  osmol). The relation between mM and mOsm is as follows: mOsm = mM  $\times$  number of particles produced by dissociation of 1 molecule.

Osmolarity is a term denoting mOsm /unit volume (mOsm /L  $\text{H}_2\text{O}$ ). Osmolarity denotes mOsm /unit weight (mOsm /Kg  $\text{H}_2\text{O}$ ). Osmolarity of a body fluid may be determined experimentally by measuring freezing point depression or one of the other colligative properties (vapor pressure, boiling point or osmotic pressure).

The total osmolarity of a solution is equal to the sum of the individual concentrations of all freely dissolved (i.e. osmotically active) solutes present in the solution. All solutes contribute equally to osmolarity simply as a function of the number of individual particles each one contributes. The total osmolarity of extracellular water (ECW) illustrates this relationship:

Total ECW osmolarity =  $1.85 \text{ Na}^+ + 0.36 \text{ NPN} + 0.06 \text{ glucose} + 10$  where  $\text{Na}^+$  refers to the serum sodium concentration in mEq /L. (Because of secondary factors, the osmotic coefficient for sodium salts is 1.85 rather than 2.) NPN refers to mg /100 ml, and the multiplication factor 0.36 converts the concentration unit to mOsm of urea/L of serum water. Glucose refers to mg /100 ml concentration and the multiplication factor 0.06 converts the concentration unit to mOsm of glucose/L of serum water. The remaining osmotically active solutes consisting of  $\text{K}^+$ ,  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$  salts and organic acids yield approximately 10 mOsm of solute/L. If normal values for  $\text{Na}^+$ , NPN and glucose are inserted into the equation, the following normal numerical contributions to ECW osmolarity are found:

Total ECW osmolarity =  $285 \text{ mOsm /L}$   
 $260 + 15 + 5 + 10$ . It is readily apparent that sodium salts constitute the bulk of ECW osmolarity. Furthermore, since  $\text{H}_2\text{O}$  is distributed in the body purely by osmosis, osmotic equilibrium exists in all parts of body water and the osmolarity of normal body water in all compartments is identical, i.e. approximately  $285 \text{ mOsm /L}$ .

In clinical parlance the term isotonic applies to solutions which have the same osmolarity as the normal body water. Similarly, hypertonic applies to solutions of higher osmolarity than body water and hypotonic applies to solutions of lower osmolarity than body water.

## WATER & ELECTROLYTE PHYSIOLOGY

### DISTRIBUTION OF WATER & ELECTROLYTES IN THE BODY

The total body water (TBW) consists of extracellular and intracellular water (ECW and ICW). The ECW, in turn, is composed of plasma, interstitial water (ISW), gastrointestinal water, and bone and connective tissue water. For the purposes of this discussion, however, the ECW is considered to mean effective extracellular fluid volume and as such consists only of the ISW and plasma. Transcellular water is a small fraction of TBW which has been processed by cells. It includes primarily CSF and gastrointestinal water. The distribution of water and electrolytes among the various anatomic compartments is shown on p. 12.

TBW is expressed as percentage of body weight in Kg. It varies with sex and body fat content. Less tissue contains the bulk of TBW, so that lean muscular males have the highest percentage values and obese females the lowest. The TBW in males varies between 55-60% of body weight; in females, 47-52% body weight.

The plasma volume is fairly uniform at 4-5% body weight. It is maintained by the balance between 2 forces: the plasma oncotic pressure exerted by the nondiffusible plasma proteins and the net hydrostatic pressure at the capillary wall. The osmolarity contributed by plasma protein is small (1 mOsm/L), but it is important because it establishes an osmotic pressure differential between plasma and interstitial fluid. All electrolytes in the effective extracellular fluid (ISW and plasma) except the plasma proteins are freely diffusible throughout the ECW compartment.

The ICW differs markedly in chemical composition from the ECW. This difference is probably maintained by 2 factors: (1) energy-consuming biologic pumps in all cell membranes, which keep the  $K^+$  in the ICW and the  $Na^+$  in the ECW, and (2) the differences in permeability of cell membranes to different anions.

The electrolyte composition of the gastrointestinal fluids varies markedly, but they are nevertheless all iso-osmotic with respect to plasma. Normally, nearly all of the gastrointestinal fluids are reabsorbed, however, in disease states large quantities may be lost. The volume of gastrointestinal fluids produced daily and their composition at various levels of the gastrointestinal tract are given on p. 41.

### OSMOTIC INTERRELATIONS BETWEEN ~ BODY SODIUM, POTASSIUM & WATER

Since cell membranes are freely permeable to water, the body water is distributed in the various anatomic compartments in osmotic equilibrium.

Although body water is organized in a complex set of compartments, for the purposes of simplification it can be divided into extracellular water (ECW) and intracellular water (ICW). The rationale of this simplification is to be found in the fact that sodium salts constitute the bulk of osmotically active solute in ECW, whereas potassium salts constitute the bulk of osmotically active solute in ICW. Furthermore, almost all other solutes present in body water can be considered to be either freely diffusible between ICW and ECW (such as urea) or osmotically inactive (such as ICW magnesium which is largely bound to protein) and consequently do not exert an effective osmotic pressure in either compartment, i.e., they do not produce an osmotic gradient because their osmolar concentration is equal in both compartments.

Since sodium and potassium salts are the major osmotically active solutes and are confined to the ECW and ICW respectively, their distribution will be decisive in determining the distribution of body water owing to the passive movement of water across cell membranes by osmosis, and the osmolar concentration of sodium in ECW will be approximately equal to the osmolar concentration of potassium in ICW.

Several very important relationships between the  $Na^+$  and body content of  $Na^+$ ,  $K^+$ , and water can be derived from the osmotic relationships described on p. 15.

Equation (h) has important physiologic and clinical implications. It states that the concentration of serum sodium is determined by the concentration of total osmotically active cation in the total body water and that abnormalities of  $Na^+$  can be best understood from changes in the body content of sodium, potassium, and water which may be induced by a disease process. The following possible exceptions to this general relationship should be noted: (1) Acute and marked hyperglycemia represents the addition of osmotically active solute to the ECW which may cause a transient osmotic transfer of water into the ECW and may lower the  $Na^+$  without a change in body content of sodium, potassium, and water. (2) Hyperlipemia will cause a spuriously low measurement of the  $Na^+$  because the lipids occupy appreciable volume in the plasma sam-

# Interrelationships Between $\text{Na}_g^+$ , Body $\text{Na}^+$ , Body $\text{K}^+$ , Body Water, ECW, & ICW Volumes

Cation concentrations refer to osmolar concentrations, the chemical concentration of the  $\text{Na}_g^+$  is essentially equal to the osmolar concentration

$$(a) \text{Na}_g^+ = [\text{Na}^+] \text{ECW, i.e., } \text{Na}_g^+ = \text{concentration } \text{Na}^+ \text{ in ECW}$$

$$(b) \text{Na}_g^+ = [\text{K}^+] \text{ICW, i.e., } \text{Na}_g^+ = \text{concentration } \text{K}^+ \text{ in ICW}$$

$$(c) \text{Na}_g^+ = \frac{\text{Total Na}^+ \text{ dissolved in ECW } (\text{Na}_{ec}^+)}{\text{Volume ECW}} = \frac{\text{Na}_{ec}^+}{\text{ECW}} \quad \text{from equation (a)}$$

$$(d) \text{Na}_g^+ = \frac{\text{Total K}^+ \text{ dissolved in ICW } (\text{K}_{ic}^+)}{\text{Volume ICW}} = \frac{\text{K}_{ic}^+}{\text{ICW}} \quad \text{from equation (b)}$$

$$(e) \text{ECW} = \frac{\text{Na}_{ec}^+}{\text{Na}_g^+} \quad \text{equation (c) solved for ECW}$$

$$(f) \text{Na}_g^+ = \frac{\text{K}_{ic}^+}{\text{TBW} - \text{ECW}} \quad \text{restatement of equation (d) in which ICW is defined as (TBW - ECW)}$$

$$(g) \text{Na}_g^+ = \frac{\text{K}_{ic}^+}{\text{TBW} - \frac{\text{Na}_{ec}^+}{\text{Na}_g^+}} \quad \text{restatement of equation (f) in which ECW is defined from equation (e)}$$

$$(h) \text{Na}_g^+ = \frac{\text{Na}_{ec}^+ + \text{K}_{ic}^+}{\text{TBW}} \quad ; \text{ algebraic simplification of equation (g)}$$

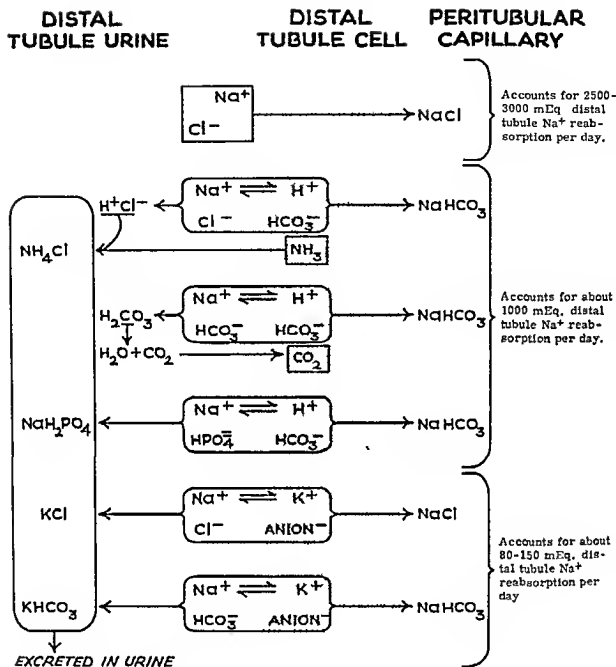
$$(i) \text{ECW} = \frac{\frac{\text{Na}_{ec}^+}{\text{C}^+}}{\frac{\text{Na}_{ec}^+ + \text{K}_{ic}^+}{\text{TBW}}} \quad \text{restatement of equation (e) in which } \text{Na}_g^+ \text{ is defined as } \frac{\text{Na}_{ec}^+}{\text{C}^+} \text{ and } (\text{Na}_{ec}^+ + \text{K}_{ic}^+) \text{ is defined as total osmotically active body cation } (\text{C}^+)$$

$$(j) \text{ECW} = \frac{\text{Na}_{ec}^+}{\text{C}^+} (\text{TBW}) \quad \text{algebraic simplification of equation (i)}$$

$$(k) \text{ICW} = \frac{\text{K}_{ic}^+}{\text{Na}_g^+} \quad ; \text{ equation (d) solved for ICW}$$

$$(l) \text{ICW} = \frac{\text{K}_{ic}^+}{\text{C}^+} \quad \cdot \text{ by substitution from equation (h)}$$

$$(m) \text{ICW} = \frac{\text{K}_{ic}^+}{\text{C}^+} (\text{TBW})$$



**Interrelationships Between  $\text{H}^+$ - $\text{Na}^+$  Exchange,  $\text{K}^+$ - $\text{Na}^+$  Exchange, &  $\text{NaCl}$  Absorption in Over-all Distal Tubular Reabsorption of  $\text{Na}^+$  in the Normal State.** The magnitude of  $\text{Na}^+$  reabsorption by each of the 3 mechanisms indicated in the diagram is only a rough approximation based on an average normal glomerular filtration rate, assuming that 80% of the filtered load of  $\text{Na}^+$  is reabsorbed with no change in the ratio of  $\text{Cl}^-$  to  $\text{HCO}_3^-$  in the proximal tubule and assuming an 80-150 mEq. dietary load of  $\text{K}^+$  requiring renal excretion. The tubule cell source of  $\text{H}^+ + \text{HCO}_3^-$  is the hydration of  $\text{CO}_2$  gas which is present in the cell in abundance in association with carbonic anhydrase, which catalyzes the  $\text{CO}_2$  hydration reaction.

ple pipetted for analysis. The concentration of  $\text{Na}_g^+$  in serum water, however, is normal in hyperlipemic states if there is no abnormality of body sodium, potassium, and water (3). Theoretically, there might be a change in the osmotic activity of sodium or potassium in disease that would alter the general relationship of  $\text{Na}_g^+$  to body content of sodium, potassium, and water. The evidence in the literature is conflicting on this point. Some studies have indicated that this does not occur, that nearly all of the intracellular potassium is osmotically active and is never inactivated. Other studies have suggested that in certain disorders sizable quantities of intracellular potassium may be inactivated (possibly by being bound to intracellular protein and hence removed from free solution) and may result in hyponatremia without a change in body content of sodium, potassium, or water.

Equation (j) states the important conclusion that the volume of ECW is directly related to the body sodium content and is influenced also by the ratio of body sodium to osmotically active cation and the TBW.

Equation (m) states the important conclusion that the volume of ICW is directly related to the body potassium content and the ratio of body sodium to osmotically active cation and the TBW.

The above interrelationships between  $\text{Na}_g^+$ , ECW volume, ICW volume, and body content of sodium, potassium, and water are simple consequences of osmotic equilibrium throughout body water, and the anatomic confinement of sodium to ECW and potassium to ICW by energy-consuming cation pumps in cell membranes. It is important to bear in mind the role of these osmotic relationships in the physiologic regulation of body sodium, potassium, and water.

### PHYSIOLOGIC REGULATION OF WATER & SODIUM

The normal physiologic regulation of water and sodium metabolism is primarily directed toward the preservation of 3 separate but related parameters of body water: (1) Osmolarity of TBW, (2) ECW volume, and (3) ICW volume.

#### Regulation of Osmolarity of TBW.

As has been indicated earlier, the osmolarity of body water is closely correlated with the  $\text{Na}_g^+$ , which in turn is determined by the ratio of body cation to body water content. The following mechanisms are involved in the

response to hyperosmolarity and hyposmolarity.

Hyperosmolarity or hypernatremia induced by loss of water results in an increased concentration of body cation. An integrated neuroendocrine-renal response occurs which consists of activation of the sense of thirst and secretion of antidiuretic hormone (ADH) from the posterior pituitary gland. The action of ADH on the kidney results in the excretion of a small volume of concentrated urine, i.e., water conservation.

Hyposmolarity or hyponatremia induced by water loading decreases the concentration of body cation in body water. The integrated neuroendocrine renal response consists of suppression of the sense of thirst and inhibition of ADH secretion. The absence of ADH results in the excretion of a large volume of dilute urine, i.e., water diuresis.

It is important to note that the primary physiologic response to an abnormality of body water osmolarity (i.e., abnormality of  $\text{Na}_g^+$ ) is appropriate adjustment of water excretion in the urine.  $\text{Na}^+$  excretion in the urine is not primarily adjusted to preserve a normal  $\text{Na}_g^+$ .

#### Regulation of ECW Volume.

As discussed on p 15, ECW volume is directly related to the body  $\text{Na}^+$  content and influenced also by the ratio of body  $\text{Na}^+$  to  $\text{C}^+$  and the TBW in accordance with the following relationship:

$$(j) \text{ ECW} = \frac{\text{Na}^+}{\text{C}^+} (\text{TBW})$$

A decrease in ECW volume leads to an integrated neuroendocrine-renal response which consists of thirst, increased secretion of aldosterone, increased secretion of ADH, and variable decrease in glomerular filtration rate. The integrated effect of this on the kidney is oliguria with excretion of a concentrated urine, which has a very low concentration of sodium and a high concentration of potassium.

This renal response occurs irrespective of any abnormality in osmolarity or  $\text{Na}_g^+$  which may appear during the pathogenesis of ECW contraction. If isotonic loss of sodium and water occurs, there will be a normal  $\text{Na}_g^+$ . If relatively pure  $\text{Na}^+$  depletion occurs, the ECW contraction will be associated with hyponatremia. If large water losses occur, the ECW contraction will be associated with hypernatremia. In each of these instances the renal response will be the same and osmolarity of body water may be sacrificed to the preservation of ECW volume.

An increase in ECW volume also leads to an integrated neuroendocrine-renal response

which consists of decreased aldosterone and ADH secretion and a variable increase in glomerular filtration rate. The effect of this response on the kidney is polyuria, sodium is present in the urine in isotonic proportion to water and the potassium in the urine tends to diminish. As shown in equation (j) sodium and water diuresis with potassium conservation will be most effective in decreasing ECW volume. As is true in ECW contraction, the mechanisms which reduce an expanded ECW volume will take precedence over osmolarity control if these 2 abnormalities occur simultaneously. Water loading in a patient who for any reason is unable to excrete the water load will eventuate in expansion of ECW and  $\text{Na}^+$  diuresis even though water diuresis cannot accompany the  $\text{Na}^+$  diuresis and hyponatremia may result.

#### Regulation of ICW Volume.

The volume of ICW is directly related to the body  $\text{K}^+$  content and influenced also by the ratio of body  $\text{K}^+$  to cation and by the TBW, as shown in equation (m)

$$\text{ICW} = \frac{\text{K}^+}{\text{C}^+} (\text{TBW})$$

An indirect neuroendocrine-renal mechanism is involved in the regulation of ICW volume. In health the volume and osmolarity of ICW are maintained by active cell metabolism, which provides energy for the intracellular accumulation of potassium and other solutes, and by the renal adjustment of water, sodium, and potassium excretion involved in the regulation of body water osmolarity and ECW volume. Primary disorders of ICW volume and osmolarity are usually the result of chronic illness and malnutrition in which intracellular  $\text{K}^+$  is lost. With acute water and electrolyte disturbances, the abnormality of ICW volume is usually secondary to abnormality of ECW volume and osmolarity. For example, with  $\text{Na}^+$  depletion in excess of associated water depletion, contraction of both ECW and ICW occur and the renal response is to conserve water and sodium and excrete potassium, which leads to a further decrease of ICW volume.

In summary it may be stated that osmolarity (or  $\text{Na}^+$ ) regulation are achieved primarily through adjustment of water excretion in the urine, ECW volume regulation is achieved through an integrated adjustment of  $\text{Na}^+$ ,  $\text{K}^+$  and water excretion in the urine, ICW volume is autonomously determined by active cellular accumulation of potassium and renal excretion of potassium and water, when more than one of these parameters of body water are threatened

simultaneously, the order of preservation is (1) ECW volume, (2) osmolarity of body water, and (3) ICW volume. The preservation of ECW volume before the other 2 is probably related to the need to preserve plasma volume and hence the circulating blood volume.

### PHYSIOLOGIC REGULATION OF POTASSIUM

Potassium salts constitute the bulk solute of intracellular water. Normal regulation of potassium in the body is directed toward the accumulation and preservation of a large quantity and high concentration of intracellular potassium and toward the precise maintenance of a much smaller quantity and lower concentration of serum potassium.

The total body content of potassium ranges from 40-50 mEq./Kg. in men, with the higher concentrations found in young muscular men and the lower in older men with smaller muscle mass. The total body content of potassium in women ranges from 30-38 mEq./Kg. with a smaller content found in older or obese women. The generally lower body potassium content in women when expressed on a per Kg. basis is due to the fact that women have a smaller muscle mass and larger fat mass than men. The potassium content per liter of body water is the same in both men and women.

The very small amount of potassium in extracellular water in contrast to the large quantity in intracellular water can be illustrated by considering the quantities present in an average, muscular young 70 Kg. male. The total body potassium would be about 3500 mEq. Assuming an ICW volume of 33% body weight and the chemical concentration of ICW  $\text{K}^+$  to be 150 mEq./L., the total  $\text{K}^+$  in intracellular water would be approximately 3440 mEq. Assuming a total extracellular fluid volume of 27% of body weight and a  $\text{K}^+$  concentration of 4 mEq./L., the total  $\text{K}^+$  in this compartment would be approximately 75 mEq. while in the plasma compartment the total  $\text{K}^+$  present would be only 12 mEq. It is apparent that only a small fraction of the total body  $\text{K}^+$  is present in extracellular water.

The normal content and distribution of potassium in body water is achieved by the combination of appropriate adjustment of renal excretion of potassium and active transport mechanisms which accumulate potassium in the intracellular water.

The kidney can vary the amount of potassium excreted in the urine over a wide range

in response to changes in  $K^+$  intake. A healthy person ingesting an average diet will excrete 80-150 mEq of  $K^+$  in the urine. If  $K^+$  is completely eliminated from the diet, renal excretion of  $K^+$  continues initially with a loss of 30-40 mEq/day in the urine. Renal conservation gradually becomes more efficient, so that by the end of 2 weeks urinary loss falls to 3-4 mEq/day. The kidney is also capable of excreting very large amounts of potassium, in individuals ingesting certain vegetarian diets the renal excretion of ingested potassium may exceed 800 mEq/day.

This remarkable flexibility of renal  $K^+$  excretion in health can be seriously disturbed in a wide variety of fluid and electrolyte and acid-base disorders, so that renal  $K^+$  excretion becomes inappropriately decreased or increased. The physiologic basis for inappropriate renal  $K^+$  excretion can be best understood from a consideration of the mechanism of  $K^+$  excretion by the kidney.

Potassium is freely filtered across the glomerulus with the total filtered load approximating 700 mEq/day. However, most (if not all) of the filtered  $K^+$  is reabsorbed in the proximal tubules so that changes in the rate of filtration of  $K^+$  not important in adjusting the amount excreted in the urine.

All (or nearly all) of the  $K^+$  found in the urine derives from the distal tubule cells, where  $K^+$  is actively secreted into the tubular urine. Potassium secretion appears to be coupled with  $Na^+$  reabsorption as an ion exchange process so that for each  $K^+$  ion secreted a  $Na^+$  ion is reabsorbed. While  $K^+-Na^+$  exchange accounts for the  $K^+$  excreted in the urine, the amount of  $Na^+$  reabsorbed by this mechanism in ordinary circumstances constitutes a small fraction of the total amount of  $Na^+$  reabsorbed in the distal tubule. There are 2 other mechanisms for  $Na^+$  reabsorption in this region of the nephron which ordinarily account for the bulk of  $Na^+$  reabsorption: (1) Reabsorption of  $NaCl$  and (2) reabsorption of  $Na^+$  in exchange for secreted  $H^+$ . Thus there are three mechanisms for  $Na^+$  reabsorption in the distal tubule of which  $K^+-Na^+$  exchange is one. These are illustrated on p 16.

The potassium secretory mechanism operates as a part of the overall process of  $Na^+$  reabsorption in the distal tubule. At least 4 important determinants of the magnitude of  $K^+$  secretion can be identified.

(1) Adrenal steroids. The mineralocorticoids greatly enhance the mechanisms for  $Na^+$  reabsorption in the distal tubule and cause  $Na^+$  retention, enhanced  $H^+$  secretion, and enhanced  $K^+$  secretion.

(2) Relative availability of  $H^+$  and  $K^+$ . Hydrogen and potassium ions in the distal tu-

bule cell appear to compete with each other for exchange with sodium ions in distal tubular urine. When  $H^+$  is in abundance, there will be increased  $H^+-Na^+$  exchange and decreased  $K^+-Na^+$  exchange. In metabolic acidosis with an absolute increase in extracellular  $[H^+]$ , accelerated  $H^+-Na^+$  exchange enhances renal excretion of acid but may decrease renal ability to secrete  $K^+$  in alkalotic disorders, although extracellular  $[H^+]$  is reduced below normal, concomitant  $K^+$  depletion may make  $K^+$  even less available in the distal tubule cell so that  $H^+-Na^+$  exchange is favored over  $K^+-Na^+$  exchange. Enhanced  $H^+$  secretion into the urine can greatly worsen such alkalotic disorders. Primary loss of  $K^+$  will lead to an increase in  $H^+-Na^+$  exchange and systemic alkalosis.

When  $K^+$  is available in abundance,  $K^+$  secretion is favored over  $H^+$  secretion. Administration of large amounts of  $K^+$  can reduce  $H^+-Na^+$  exchange and lead to systemic acidosis. In alkalotic disorders associated with the loss of  $HCl$ ,  $H^+$  secretion is inhibited while  $K^+$  secretion is accelerated. This results in an appropriately alkaline urine but loss of large quantities of  $K^+$ .

(3) Concentration of  $Cl^-$  in the distal tubular urine. There is recent evidence indicating that  $[Cl^-]$  in distal tubular urine may strongly affect both  $H^+-Na^+$  and  $K^+-Na^+$  exchange. It appears that both exchange mechanisms are accelerated when there is a decrease in  $[Cl^-]$  in distal tubular urine. In metabolic alkalosis with hypochloremia the correction of the hypochloremia itself is an important therapeutic maneuver which will decrease the rate of  $H^+$  and  $K^+$  secretion in the distal tubule.

(4) Availability of  $Na^+$ . Since  $K^+$  secretion is dependent upon distal tubular  $Na^+$  reabsorption, it is apparent that  $K^+$  secretion will be influenced by the total amount of  $Na^+$  presented to the distal tubule. When  $Na^+$  reabsorption is nearly complete in the proximal tubule such as might occur with a marked fall in filtration rate,  $K^+$  secretion will be impaired because inadequate  $Na^+$  reaches the distal tubular exchange site. When abundant  $Na^+$  reaches the distal tubule, the magnitude of  $K^+$  secretion is determined by the other factors described above.

The normal distribution of  $K^+$  in body water is achieved by cellular transport mechanisms. As was discussed above, normally the concentration of  $K^+$  in ICW is approximately 150 mEq/L while the  $K^+$  concentration in ECW averages 4 mEq/L. In view of this high ICW  $K^+$  concentration and the large volume of ICW, disturbances in the cell membrane trans-

port process for  $K^+$  can lead to marked changes in ECW  $K^+$  concentration due to faulty distribution.

#### Metabolic Acidosis.

Metabolic acidosis causes movement of  $K^+$  into ECW which characteristically results in hyperkalemia. Potassium depletion in metabolic acidosis is frequently associated with normal or elevated  $K_s^+$  because of this abnormality in distribution. Impaired renal secretion of  $K^+$  in acidosis tends to sustain the hyperkalemia.

#### Metabolic Alkalosis.

Metabolic alkalosis is associated with a tendency to retain  $K^+$  in ICW and a loss of  $K^+$  in the urine which results in hypokalemia and a concomitant abnormality in distribution. In some cases hypokalemia may be present with minimal  $K^+$  depletion in metabolic alkalosis.

#### Respiratory Acidosis.

Respiratory acidosis produces changes similar to those in metabolic acidosis except that the abnormality in distribution of  $K^+$  and the degree of hyperkalemia are often less marked.

#### Respiratory Alkalosis.

Respiratory alkalosis produces changes similar to those in metabolic alkalosis except that here again the abnormality in distribution of  $K^+$  and the degree of hypokalemia are often less marked.

#### Chronic Illness & Malnutrition.

These states are thought to frequently result in defective cell membrane transport of  $K^+$  so that  $K^+$  is lost from the ICW in large amounts. The  $K_s^+$  is often normal or only mildly elevated because of adequate renal secretion of the  $K^+$  which is "leaked" into the ECW. A major manifestation of these disorders of  $K^+$  distribution is hyponatremia due to the loss of osmotically active potassium salts (see discussion on p. 27).

### ACID-BASE METABOLISM

The normal body fluids are maintained in a slightly alkaline state by rigid control of hydrogen ion concentration, or  $[H^+]$ . The control of  $[H^+]$  is achieved through the action of the buffers present in body fluids and respiratory and renal operations on the buffers.

#### Hydrogen Ion Concentration, or $[H^+]$ .

An acid is an electrolyte which dissociates in solution to yield  $H^+$  and anion. A base is an electrolyte which dissociates to yield cation and  $OH^-$ . A salt is the product of a chemical reaction between an acid and a base in which  $H^+$  and  $OH^-$  form  $H_2O$ , leaving the cation and anion in solution. Weak acids and weak bases are only partially dissociated in solution, strong acids and strong bases are entirely dissociated.

In a neutral solution the  $H^+$  concentration ( $[H^+]$ ) and the  $OH^-$  concentration ( $[OH^-]$ ) are equal. In an acid solution  $[H^+] > [OH^-]$ , and in an alkaline solution  $[OH^-] > [H^+]$ . The  $[H^+]$  of body fluids is extremely small, on the order of  $10^{-7}$  M/L. For ease of calculation it is expressed as pH, which is the negative logarithm of the  $[H^+]$ .

The pH of the body fluids is defined as the concentration ratio of salt to weak acid

$$pH = pK + \log \frac{\text{salt}}{\text{acid}},$$

where pK is the negative logarithm of the dissociation constant of the weak acid. This is known as the Henderson-Hasselbalch equation. For  $H_2CO_3$ , pK is 6.1.

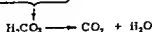
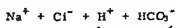
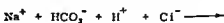
In health the plasma pH is  $7.40 \pm 0.05$ . This narrow range is maintained by a combination of body fluid buffers under the influence of respiratory and renal mechanisms.

#### Body Fluid Buffers.

A buffer is any substance in solution which resists a change in pH of the solution when a strong acid or strong base is added. All solutions of weak acids or bases and their salts have this tendency to maintain a constant pH.

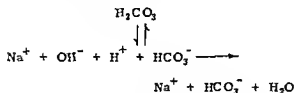
The buffer pairs of the body fluids are all weak acids and their highly dissociated salts. The important buffer systems are  $NaHCO_3$ ,  $H_2CO_3$ ,  $Na$ -Protein,  $H$ -Protein, hemoglobin,  $H$ -Hemoglobin, and  $Na_2HPO_4$ ,  $NaH_2PO_4$ . Strong acids are buffered by the highly dissociated salts, and strong bases are buffered by the weak acids. Total buffer capacity is the sum of the buffer salts capable of accepting  $H^+$  or the buffer acids capable of contributing  $H^+$ .

These buffer reactions can be illustrated by considering the  $NaHCO_3$ ,  $H_2CO_3$  buffer pair, which is the most important ECW buffer system. If a strong acid is added to the system, the following equilibrium results:





If a strong base is added to the system, the result is as follows



In this case the strong base (NaOH) is buffered by the weakly dissociated acid,  $\text{H}_2\text{CO}_3$ , with the formation of the highly dissociated salt,  $\text{NaHCO}_3$ , and water

With the addition of a strong acid, the ratio  $\text{NaHCO}_3 \cdot \text{H}_2\text{CO}_3$  decreases ( $[\text{H}_2\text{CO}_3]$  increases), whereas with the addition of NaOH, the ratio increases ( $[\text{NaHCO}_3]$  increases). Therefore, there will be some change in pH, but this change is much less than if the buffer had not been present

#### Effect of $\text{CO}_2$ Content on pH.

Clinical evaluation of acid-base disorders is based primarily on examination of the bicarbonate buffer system. Most clinical laboratories report either a total plasma  $\text{CO}_2$  content or a  $\text{CO}_2$  combining power (total plasma  $\text{CO}_2$  at arbitrary  $\text{pCO}_2$  of 40 mm Hg). The  $\text{pCO}_2$  refers to the partial pressure of the [dissolved  $\text{CO}_2$ ] in the plasma and is directly related to the [dissolved  $\text{CO}_2$ ]. The normal value for total  $\text{CO}_2$  is 28 mM/L. Its normal chemical partition and its relationship to pH can be illustrated as follows

$$\begin{aligned} \text{pH} &= \text{pK} + \log \frac{[\text{salt}]}{[\text{acid}]} \\ &= \text{pK} + \log \left[ \frac{[\text{NaHCO}_3]}{[\text{H}_2\text{CO}_3] + [\text{dissolved CO}_2]} \right]^* \\ &= 6.1 + \log \frac{26.70 \text{ mM/L}}{0.02 \text{ mM/L} + 1.28 \text{ mM/L}} \\ &= 6.1 + \log 20 \\ &= 6.1 + 1.3 \\ &= 7.4 \end{aligned}$$

Therefore, as long as the molar ratio  $[\text{NaHCO}_3] : [\text{H}_2\text{CO}_3]$  remains at approximately

20:1, the pH of the body fluids will be maintained at 7.4 regardless of the total plasma  $[\text{CO}_2]$ . An absolute increase in the ratio ( $[\text{NaHCO}_3]$  increased or  $[\text{H}_2\text{CO}_3]$  decreased) results in alkalosis ( $\text{pH} > 7.45$ ), conversely, an absolute decrease in the ratio results in acidosis ( $\text{pH} < 7.35$ ).

#### Respiratory Control of Acid-Base Balance.

The concentration of  $\text{CO}_2$  gas (and  $\text{H}_2\text{CO}_3$ ) is directly controlled by the depth and rate of ventilation. Metabolic acidosis (in which  $\text{HCO}_3^-$  is converted to  $\text{H}_2\text{CO}_3$  or where  $\text{HCO}_3^-$  is lost directly) is compensated by hyperventilation to increase  $\text{CO}_2$  excretion and lower  $\text{pCO}_2$  in an attempt to maintain a 20:1  $[\text{NaHCO}_3] : [\text{H}_2\text{CO}_3]$  ratio with a decreased total  $[\text{CO}_2]$ . Metabolic alkalosis (due to addition of  $\text{HCO}_3^-$ ) is partially compensated by hypoventilation with a rise in  $\text{pCO}_2$  to maintain the  $[\text{NaHCO}_3] : [\text{H}_2\text{CO}_3]$  ratio near 20:1 with an increased total  $[\text{CO}_2]$ .

#### Renal Control of Acid-Base Balance.

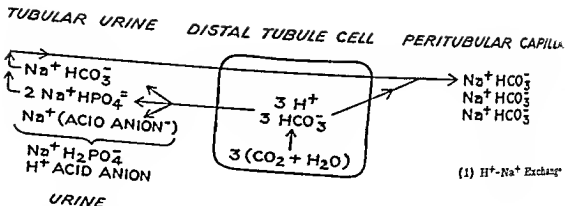
The kidney is primarily responsible for the regulation of plasma  $[\text{NaHCO}_3]$ . Broadly considered, this is accomplished by regulation of reabsorption of the filtered  $\text{NaHCO}_3$  and by regeneration of  $\text{HCO}_3^-$  by cell metabolism.

In the proximal tubules approximately 80% of the glomerular filtrate is reabsorbed. This is accomplished primarily through active  $\text{Na}^+$  reabsorption followed by passive osmotic movement of water. Since there is little change in pH of the filtrate in the proximal tubule, the  $\text{HCO}_3^-$  concentration of the filtrate remains relatively unchanged as it passes into the distal tubule. It follows that about 80% of the filtered load of  $\text{NaHCO}_3$  is reabsorbed in the proximal tubule and returned to the plasma. Although this actually represents the bulk of  $\text{NaHCO}_3$  reabsorption in the kidney and is essential to avoid massive  $\text{NaHCO}_3$  depletion, the precise control of plasma  $\text{HCO}_3^-$  is achieved via the regulation of  $\text{HCO}_3^-$  transport across the distal segment of the nephron.

About 20% of the glomerular filtrate reaches the distal tubule, where 3 mechanisms can be defined which operate to control plasma  $[\text{NaHCO}_3]$ . They are intimately related to  $\text{Na}^+$  reabsorption and  $\text{K}^+$  secretion: (1)  $\text{H}^+ \text{Na}^+$  exchange, (2) tubular secretion of  $\text{NH}_3$  and (3) suppression of  $\text{H}^+$  and  $\text{NH}_3$  secretion.

In mechanism (1),  $\text{H}^+$  derived from the hydration of  $\text{CO}_2$  in the distal tubule cell is secreted in exchange for  $\text{Na}^+$  from the tubular urine. The  $\text{Na}^+$  reabsorbed from the tubular urine and  $\text{HCO}_3^-$  from the distal tubule cell are returned to the plasma. The fate of the secreted  $\text{H}^+$  varies depending upon the anion present with  $\text{Na}^+$  in the tubular urine. If the

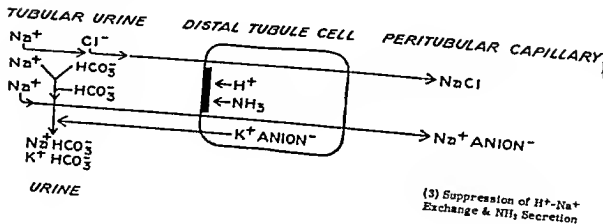
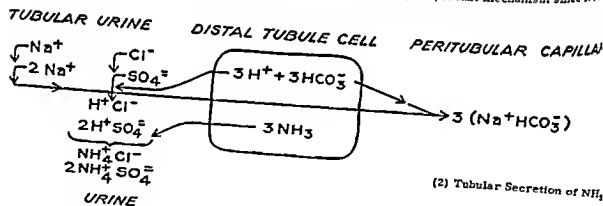
\*Actually, the acid form of this buffer pair exists mostly as dissolved  $\text{CO}_2$  gas. For convenience,  $[\text{H}_2\text{CO}_3]$  as used hereafter will mean the sum of  $[\text{H}_2\text{CO}_3]$  and  $[\text{dissolved CO}_2]$ .



anion is  $\text{HCO}_3^-$ .  $\text{H}_2\text{CO}_3$  is formed which rapidly dehydrates to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  and the  $\text{CO}_2$  diffuses back into the cell. If the anion is  $\text{HPO}_4^{2-}$ , the  $\text{H}^+$  is carried out in the urine as  $\text{H}_2\text{PO}_4^-$ . If some other weak acid anion is present it is carried out in the urine as  $\text{H}^+$  Anion. The net effect of  $\text{H}^+ - \text{Na}^+$  exchange has been to both reabsorb and regenerate  $\text{NaHCO}_3$  for the plasma. This mechanism is enhanced in metabolic

acidosis, where the plasma  $[\text{NaHCO}_3]$  is low or in respiratory acidosis, where  $[\text{H}_2\text{CO}_3]$  is increased.

In mechanism (2) the distal tubule cells secrete  $\text{NH}_3$  into the tubular urine. The  $\text{NH}_3$  combines with secreted  $\text{H}^+$  to form  $\text{NH}_4^+$  which is then excreted with strong acid anions such as  $\text{Cl}^-$  and  $\text{SO}_4^{2-}$ . The formation of  $\text{NH}_4^+$  is an exceedingly important mechanism since it



the concentration of free  $H^+$  in the urine under these circumstances. Distal tubular cells secrete  $H^+$  into the urine after the reaction (4), therefore, the continued reabsorption of  $[H^+]$  by formation of  $NH_4$  greatly increases the total amount of  $H^+$  that can be secreted. This mechanism also operates in both metabolic and respiratory acidosis to reabsorb and regenerate  $NaHCO_3$ .

Mechanism (3) represents suppression of  $Na^+$  exchange and  $NH_3$  secretion associated with accelerated  $K^+-Na^+$  exchange. There is enhanced  $Na^+$  reabsorption as  $NaCl$ . The effect of this distal tubular response is the excretion of large quantities of  $NaHCO_3$  and  $CO_2$  in the urine. This mechanism operates in metabolic alkalosis, where the plasma  $NaHCO_3$  is increased, or in respiratory alkalosis where the  $H_2CO_3$  is decreased.

It should be noted that enhanced  $H^+-Na^+$  exchange and  $NH_3$  secretion cause the excretion of an acid urine, conserve  $Na^+$ , and regenerate  $NaHCO_3$  salt. To the extent that these mechanisms are inadequate in compensating for metabolic acidosis,  $Na^+$  depletion will occur because of the urinary loss of  $Na^+$  salts.

When metabolic alkalosis is compensated by suppression of  $H^+-Na^+$  exchange and  $NH_3$  secretion and enhanced  $K^+-Na^+$  exchange, large quantities of  $Na^+$  and  $K^+$  are lost as  $CO_2$  salts.

Clinical acid-base disturbances will frequently have sizable amounts of  $Na^+$ ,  $K^+$ , and water depletion from both extrarenal routes, such as vomiting or diarrhea, and also through the kidney because of the compensatory mechanism described above. Cation and water depletion impose severe limitations on renal compensatory mechanisms. For example, if  $Na^+$  and  $K^+$  depletion have complicated metabolic alkalosis, maximum  $Na^+$  reabsorption resumes in the distal tubule which must involve accelerated  $H^+-Na^+$  exchange and diminished  $K^+-Na^+$  exchange because of  $K^+$  depletion. This leads to increasing reabsorption of  $NaHCO_3$ , further rise in plasma  $NaHCO_3$ , and uncompensated metabolic alkalosis. In metabolic acidosis, cation and water depletion will lead to a fall in filtration rate and decreased delivery of  $Na^+$  salts to the distal tubule, thereby severely limiting the magnitude of  $H^+-Na^+$  exchange and  $NH_4^+$  excretion. Consequently a careful assessment of cation and water depletion is essential in the evaluation of acid-base disturbances.

The role of the lungs and kidneys in maintaining acid-base balance may be summarized as follows:

Metabolic acidosis is compensated by hyperventilation and by renal secretion of  $H^+$  and  $NH_3$ , i.e., mechanisms (1) and (2).

Metabolic alkalosis is compensated by hypoventilation and by the suppression of  $H^+$  and  $NH_3$  secretion by the kidney, i.e., mechanism (3).

Respiratory acidosis, where the lungs cannot excrete  $CO_2$ , is compensated by renal mechanisms (1) and (2).

Respiratory alkalosis, as occurs in hyperventilatory states, is compensated by renal mechanism (3).

The body fluid changes in the compensated and uncompensated phases of these disorders are summarized on p. 24.

## DIAGNOSIS & TREATMENT OF WATER, ELECTROLYTE, & ACID-BASE DISTURBANCES

It is essential to plan initial therapy carefully and to keep a systematic record of the progress of therapy. Three rules are basic in planning therapy: (1) Determine the magnitude of abnormality in volume and osmolality of body fluid (state of hydration and  $Na^+$  or abnormality in water and  $Na^+$  metabolism). (2) Determine which acid-base abnormality may be present. (3) Determine specific abnormalities in  $K^+$ ,  $Ca^{++}$ , and  $HPO_4^{--}$  levels.

It cannot be emphasized too strongly that initial therapy is based on a simultaneous consideration of the volume, osmolality, and acid-base status of the body fluids. This information is best derived from the history and physical examination, the results of laboratory tests, and an understanding of the fundamental disease process. Continuing therapy is based on accurate estimations of the daily gain or loss of fluids and electrolytes. This is best accomplished by keeping a flow sheet on which the physician can calculate the daily balances (see p. 25).

In addition to the flow sheet, it is essential to have a simple form on which the nurse can keep records of the fluids administered and output collections during each 24-hour period.

Daily weights are also best recorded by the physician and should be measured under standard conditions, i.e., at approximately the same time each day, after the patient has voided and is fasting. Changes in body weight over a short period can be considered to be equivalent to a change in total body water volume.

Changes in body content of water and electrolytes in various clinical disorders are given on p. 24.

**Relationships Between Body  $\text{Na}^+$ ,  $\text{K}^+$ , &  $\text{H}_2\text{O}$  Content & the Serum  $\text{Na}^+$  Concentration  
in the Pathogenesis of Body Fluid Volume & Osmolarity Disorders**

	Hyponatremia	Normal Serum $\text{Na}^+$	Hypernatremia
Normal hydration	(a) Depletion of body $\text{Na}^+$ with normal body $\text{K}^+$ and water content (b) Depletion of body $\text{K}^+$ with relatively normal body $\text{Na}^+$ and $\text{H}_2\text{O}$ content	Normal	(a) Excess body $\text{Na}^+$ with normal TBW (Uncommon disorder often iatrogenic)
Dehydration	(a) Depletion of body $\text{Na}^+$ and $\text{K}^+$ in excess of the depletion of body water (There are often large $\text{Na}^+$ and $\text{H}_2\text{O}$ deficits)	(a) Isotonic deficits in body $\text{Na}^+$ $\text{K}^+$ and $\text{H}_2\text{O}$ (Major deficits of $\text{Na}^+$ and $\text{H}_2\text{O}$ may be present with normal serum $\text{Na}^+$ )	(a) Pure water depletion (b) Water depletion in excess of $\text{Na}^+$ depletion (Hypernatremia and $\text{Na}^+$ depletion may co-exist)
Overhydration	(a) Body water excess without change in body $\text{Na}^+$ and $\text{K}^+$ content (b) Body water excess as associated with relatively less excess of body $\text{Na}^+$ and with depletion of body $\text{K}^+$ (c) Never due to body $\text{Na}^+$ depletion	(a) Isotonic excess in body $\text{Na}^+$ and $\text{H}_2\text{O}$	(a) Excess body $\text{Na}^+$ greater than the excess in TBW (Almost always iatrogenic)

**Biochemical Changes in Acidosis & Alkalosis†**

	Val %	mEq /L	Normal	Acidosis				Alkalosis				Val %	mEq /L
				Metabolic		Respiratory		Metabolic		Respiratory			
				U+	C+	U+	C+	U+	C+	U+	C+		
H HCO <sub>3</sub>	3	— 1.35										3	— 1.35
B HCO <sub>3</sub>	60	— 26										60	— 26
	120	— 32										120	— 32
Serum CO <sub>2</sub> content (Vol %)			53	33	31.5	66	32.6	93	94.5	61.5	31.5		
Serum pCO <sub>2</sub>			—	—	↑	↑	↑	—	↑	↓	↓		
pH			—	↓	—	↓	—	↑	—	↑	—		
Ratio of H <sub>2</sub> CO <sub>3</sub> to B HCO <sub>3</sub>			1.20	<1.20	1.20	<1.20	1.20	>1.20	1.20	>1.20	1.20		

$\text{U}^+$  = Uncompensated  $\text{C}^+$  = Compensated

†Reproduced, with permission, from Harold A. Harper, Review of Physiological Chemistry, 8th Ed Lange, 1961



## EVALUATION OF THE STATE OF HYDRATION

The most important step in the diagnosis of fluid and electrolyte disorders is a careful assessment of the body content of water or the state of hydration. Therapy always requires a decision as to the volume, concentration and composition of administered fluids, and such decisions cannot be made without knowledge of the state of hydration.

### Normal Hydration, Dehydration, & Overhydration.

The state of hydration is evaluated on the basis of the history and physical examination. If possible the history should cover fluid and electrolyte intake since the onset of illness, routes and volumes of losses, and changes in body weight. The patient should be questioned specifically about thirst. A careful history can yield invaluable information about volume and electrolyte abnormalities. A history of loss of gastrointestinal fluids suggests that isotonic cation and water deficits are likely to be present. A history of the magnitude of weight change can often be used as a reliable measure of the abnormality of body water content.

The physical examination permits direct observation of the state of hydration primarily from examination of the skin, mucous membranes, pulse, and BP. It is important to examine the skin and mucous membranes in all of the accessible regions of the body in order to properly assess the state of hydration. The following physical findings should be carefully looked for:

**A. Normal Hydration.** The skin is resilient and elastic, if picked up and released, it quickly springs back. If the patient has been in bed for a few hours, there are creases on his back from wrinkles in the sheets. The intertriginous areas are moist, and the oral and anal mucous membranes are moist and glistening.

**B. Dehydration.** The skin is doughy and fails to spring back quickly or completely. This finding appears earliest on the extremities. Creases on the back disappear. The oral and anal mucous membranes are dry and dull. With dehydration of less than 3% of the body weight, these signs may be minimal and difficult to interpret. With more severe degrees of dehydration (especially in combined water and  $\text{Na}^+$  deficit), the plasma volume decreases sufficiently to cause tachycardia and hypotension; the patient is lethargic or semicomatose and nausea and vomiting may develop.

**C. Overhydration.** The cardinal manifestation of isotonic overhydration (due to isotonic excess of  $\text{Na}^+$  and water) is edema due to an expanded ECW. It is first apparent in dependent areas, i.e., the lower legs of the ambulatory patient and in the posterior aspects of the thighs, buttocks, and sacral area of the bedridden patient. Overhydration of less than 5% of the body weight, however, may not be recognizable at the bedside.

In overhydration due to a primary excess of water, the excessive body content of water is distributed throughout all compartments, the absolute magnitude of water excess encountered clinically is usually less than the magnitude of volume excess frequently encountered in isotonic overhydration (i.e., excess ECW). For both of these reasons demonstrable edema usually does not accompany primary water excess and the patient appears to be normally hydrated. Primary excess of water (i.e., water intoxication) is manifested predominantly by hyponatremia.

### Abnormal Distribution of Water.

In addition to changes in the total body content of water, there may be an abnormal distribution of water in the following disorders: peritonitis, bowel obstruction, burns, venous obstruction, and lymphatic obstruction. These disorders cause a redistribution of ECW due to obligatory accumulation of edema in localized regions which leads to loss of ECW volume from other regions of the body. If adequate  $\text{Na}^+$  and water are provided to the patient during the pathogenesis of these disorders, isotonic retention by the kidney of the administered  $\text{Na}^+$  and water will restore the ECW deficits in regions other than the site of obligatory edema formation and also tend to increase local edema formation. If the supply of  $\text{Na}^+$  and water is inadequate, the physical signs and clinical consequences of isotonic dehydration may be found coexisting with evidence of localized edema.

### Special Problems.

In the following situations it may be difficult to evaluate the state of hydration from the appearance of the skin and mucous membranes:

**A.** In obese patients, where the skin is tightly stretched by subcutaneous fat.

**B.** In patients with chronic dermatitis, where the skin is thickened and inelastic.

**C.** In elderly patients, where the skin, especially over the extremities, is often atrophic and inelastic.

D In dyspneic patients and chronic mouth breathers, who may have dry oral mucous membranes without dehydration

E In patients who have lost a large amount of weight, the subcutaneous tissues may be thick and collapse on pressure and give a false impression of pitting.

## DIAGNOSIS & TREATMENT OF DISORDERS OF WATER & SODIUM METABOLISM

Abnormalities of water and sodium are interrelated and must be considered simultaneously. Since the clinical starting point is the state of hydration as determined by history and physical examination, these abnormalities will be categorized and discussed on the basis of the clinically determined state of hydration and the serum sodium concentration

### Disorders of Water & Sodium With Normal Hydration

A Normal  $\text{Na}^+$  The ECW volume and osmolarity are normal

B Hyponatremia The ECW volume is normal, but the body fluids are hypo-osmolar. This may result from any of the following conditions

1 Water and  $\text{Na}^+$  depletion treated by water replacement alone - This is always a consequence of inappropriate replacement and can occur in any of the situations (discussed below) which cause  $\text{Na}^+$  and water depletion. If hyponatremia is severe, hypertonic  $\text{NaCl}$  should be administered

2  $\text{K}^+$  deficiency with associated slight excess body water content - This is a common occurrence in chronic illnesses with malnutrition and is often called "asymptomatic hyponatremia". It is usually characterized by mild hyponatremia ( $\text{Na}^+ > 125 \text{ mEq/L}$ ), a normal or slightly elevated  $\text{K}^+$ , and no obvious edema. It is probably due to a defect in the ability to accumulate  $\text{K}^+$  in cell water. Therapy is usually directed against the primary disease process

3  $\text{Na}^+$  depletion due to inappropriate secretion of ADH - This syndrome is characterized by normal hydration on examination and a concentrated urine which contains excessive  $\text{Na}^+$  despite hyponatremia. In many instances the hyponatremia is mild and asymptomatic but occasionally it may be severe ( $\text{Na}^+ < 115 \text{ mEq/L}$ ). The syndrome is found in certain patients with bronchogenic carcinoma, other

metastatic tumors, cerebrovascular accidents, and head injuries. The mechanism is believed to be excessive secretion of ADH, which causes water retention and stimulation of an ECW volume receptor mechanism. This in turn causes excessive urinary  $\text{Na}^+$  excretion. The volume increase is not great enough to result in detectable edema. Treatment consists of restricting water to about 800 ml/day, which results in moderate weight loss and  $\text{Na}^+$  retention

C Hypernatremia The body fluids are hyperosmolar, but the ECW volume is normal. This combination occasionally appears in cardiac patients who have sustained extrarenal water losses, e.g., in pneumonia or with tracheostomies. It more commonly is the result of excessive use of hypertonic saline in patients with severe renal disease. To treat this condition salt restriction is of course necessary. With severe hypernatremia, e.g.,  $\text{Na}^+ > 160 \text{ mEq/L}$ , 5% dextrose in water may be indicated to restore  $\text{Na}^+$  to normal (see equation [3] below). However, this therapy involves the risk of inducing acute pulmonary edema in patients with heart disease

### Disorders of Water & Sodium With Dehydration

A Normal  $\text{Na}^+$  Osmolarity is normal but ECW volume is low. This is a common abnormality which results from isotonic losses of  $\text{Na}^+$  and water and causes selective depletion of ECW with a fall in plasma volume. The most common cause is loss of gastrointestinal fluid, which is iso-osmotic with respect to plasma.  $\text{Na}^+$  and water losses in diabetic acidosis are also usually approximately iso-osmotic and often produce a similar pattern

Therapy depends upon an estimate of the volume deficit. In some patients the change in body weight and the physical signs will be an adequate guide, in others the packed cell volume (PCV) may be helpful, provided anemia or polycythemia is not present. Marked abnormalities of body fluid osmolarity (e.g., abnormal  $\text{Na}^+$ , BUN, or glucose) will also alter the PCV

In this type of volume depletion the decrease in ECW volume is roughly proportional to the decrease in plasma volume. Using the initial known or assumed normal PCV of 45%, the volume deficit can be calculated as follows

[1]

$$\text{Liters deficit} = \frac{\text{PCV} - 0.45}{0.55 \times \text{PCV}} (0.2 \times \text{wt in Kg})^*$$

\*The ECW volume is assumed to be approximately 20% of the body weight rather than

where PCV is expressed as a decimal.

Estimates derived from the above equation are approximations only. Continued therapy is based on change in pulse rate, BP, state of hydration, PCV, weight, and urine flow

Ordinarily the dehydration is corrected by isotonic NaCl, if there is an associated severe acid-base disturbance, however, it may be desirable to administer an anion other than  $\text{Cl}^-$  with the  $\text{Na}^+$ . In addition, water and glucose are needed for insensible water losses and for calories

**B Hyponatremia** Both ECW volume and osmolarity are lost, i.e., there is combined water and sodium depletion. This abnormality is complex because there is generally an isotonic loss of  $\text{Na}^+$  and water with superimposed additional  $\text{Na}^+$  and  $\text{K}^+$  depletion. Depletion of ECW (especially plasma volume) with this abnormality is usually severe

Clinical causes of hyponatremia and dehydration include adrenal insufficiency, gastrointestinal and large sweat losses which have been partially replaced by water alone, and in renal  $\text{Na}^+$  wasting

Therapy should be directed toward correction of the isotonic deficit as well as correction of the additional  $\text{Na}^+$  and  $\text{K}^+$  depletion. In most instances the isotonic component of the salt and water deficit is large and initial replacement with isotonic NaCl is indicated, after ECW volume has been restored, the kidneys will usually correct the defect in osmolarity if adequate  $\text{Na}^+$ ,  $\text{K}^+$ , and water have been supplied. Occasionally, when the deficit in volume is relatively small (usually because of prior administration of water), the most appropriate therapy is hyperionic saline (3-5% NaCl) to correct the  $\text{Na}^+$  depletion

The isotonic salt and water deficit may be estimated from changes in body weight or approximated from equation [1]

Although  $\text{Na}^+$  is primarily an extracellular ion, its osmotic effect will be distributed throughout the TBW, as each increment of  $\text{Na}^+$  is added to the ECW, the ICW will migrate into the ECW until ICW osmolarity and ECW osmolarity are equal. Consequently the amount of  $\text{Na}^+$  to be administered must be calculated on the basis of the volume of TBW as follows

[Note continued from p. 27.]

17.5% because the actual ECW deficit will be somewhat underestimated since the increasing concentration of plasma protein will tend to preserve the plasma volume. See equation II on p. 42.

[2]

$$\text{mEq. Na}^+ = (140 - \text{Na}_s^+)(0.55 \times \text{wt. in Kg})^*$$

This estimate is based on the assumption that there has been no significant degree of  $\text{K}^+$  depletion and no significant change in  $\text{K}^+$  balance will occur during therapy

**C. Hypernatremia** Water losses have been greater than  $\text{Na}^+$  and  $\text{K}^+$  loss, with the result that a hyperosmotic state exists. The pathogenesis of this disorder falls into 2 classes

1 Water depletion without salt depletion - Primary water depletion can occur under a number of conditions: coma, cerebrovascular disease with obtunded thirst mechanisms, diabetes insipidus, thyrotoxicosis, tracheostomy patients, nephrogenic diabetes insipidus, hypercalcemia, postobstructive uropathies, and, rarely, in diarrheal disorders

Because in primary water depletion the loss is proportionate throughout the TBW, serious hypovolemia is seen only after relatively large deficits

The water deficit is estimated from the  $\text{Na}_s^+$  as follows

[3]

$$\text{Liters deficit} = \frac{\text{Na}_s^+ - 140}{\text{Na}_s^+} (0.55 \times \text{wt. in Kg})^\dagger$$

The most useful repair solution is 5% or 10% dextrose in water.

2 Water depletion in excess of  $\text{Na}^+$  depletion - Both water and salt are depleted, but the body fluids are hyperosmolar because water has been lost in excess of salt. Untreated sweat losses and losses of gastrointestinal secretions which have been complicated by insensible losses through perspiration are 2 of the common causes of hypo-osmotic salt and water loss. Osmotic diuresis caused by high-protein gavage or decompensated diabetes mellitus also may produce hypernatremia and dehydration

Usually the major deficit will be water (equation [3]), in which case 5 or 10% dextrose in water is indicated. This will restore tonicity of body fluids, although an isotonic water and salt depletion may still exist. This may be corrected with isotonic saline solution according to equation [1].

\*See equation III, p. 43.

†See equation IV, p. 43.



### Disorders of Water & Sodium With Over-hydration.

A Normal  $\text{Na}_g^+$  Osmolarity is normal, but the volume of ECW is increased. This is a common abnormality resulting from isotonic retention of  $\text{Na}^+$  and water such as occurs in congestive heart failure, nephrosis, cirrhosis, and excessive administration of isotonic saline in oliguric states. Treatment should be directed against the underlying disease. Diuretic therapy and salt restriction are commonly employed in many of these patients.

B Hyponatremia Coexistent edema and hyponatremia is a complex volume-osmolarity abnormality. The pathogenesis of this disorder differs according to whether it is chronic or acute.

1. Chronic overhydration with hyponatremia - This disorder occurs in far-advanced congestive heart failure, nephrosis, and cirrhosis. Often it is an unfavorable prognostic sign. The over-all abnormality consists of a deficiency in total body  $\text{K}^+$  and an excess of  $\text{Na}^+$  and water. The hypo-osmolarity results from the fact that there is a deficiency of  $\text{K}^+$ , and water is retained in excess of  $\text{Na}^+$ .

Treatment should be directed against the underlying disease. If, however, hyponatremia is severe ( $\text{Na}_g^+ < 118 \text{ mEq/L}$ ) and produces symptoms (e.g., mental confusion, oliguria, or severe weakness), specific correction of the hypo-osmolarity should be attempted.

The first step is rigid restriction of water intake to 800 ml/day. This alone may relieve the symptoms and restore responsiveness to diuretic therapy in 2-3 days by raising  $\text{Na}_g^+$ . If the  $\text{K}_g^+$  is less than 5 mEq/L.,  $\text{K}^+$  administration, in addition to water restriction, is indicated. A favorable response is indicated by water diuresis,  $\text{K}^+$  retention, and a rise in  $\text{Na}_g^+$ . Give 1-3 mEq. of  $\text{K}^+/\text{Kg}$  /day orally when possible, in 4 divided doses. Despite the presence of considerable  $\text{K}^+$  depletion, however, the tolerance to  $\text{K}^+$  in these states may be poor. Consequently it is essential to measure the  $\text{K}_g^+$  and ECG daily, especially early in therapy. An elevated  $\text{K}_g^+$  is an absolute contraindication to  $\text{K}^+$  administration. Oliguria is a relative contraindication, when the urine volume is  $> 350 \text{ ml./24 hours}$  and the  $\text{K}_g^+$  is  $< 5 \text{ mEq/L.}$ ,  $\text{K}^+$  administration is relatively safe and may be effective in reversing the oliguria and hypo-osmolarity.

When  $\text{K}^+$  administration is not feasible or is ineffective in reversing severe symptomatic hyponatremia, water restriction and simultaneous administration of hypertonic NaCl may be necessary. In cardiac patients such therapy must be used with caution because of the risk

of acute pulmonary edema. The total  $\text{Na}^+$  "deficit" may be calculated from equation [2]. Approximately one-third of this amount may be administered initially as 5% NaCl solution. If signs of pulmonary edema do not appear, the remaining two-thirds may be given during the next 24-72 hours if the patient continues to improve.

2 Acute overhydration with hyponatremia - Acute hyponatremia may appear in edematous patients because of water retention while on a low  $\text{Na}^+$  diet. The term "dilutional hyponatremia" has been applied to this sequence of events. After paracentesis patients with cirrhosis often retain water avidly and re-form ascites. For this reason, it is essential to restrict water intake to 1 L/day for 3 days after paracentesis. If it is necessary to support plasma volume, plasma or hyperoncotic albumin may be used without expanding body water volume.

Another common cause of acute hyponatremia is the administration of excessive quantities of water to oliguric patients. The risk of acute hyponatremia is substantial for 72 hours after surgery, when physiologic oliguria is often present. In addition, patients with acute renal failure are defenseless against the administration of water. Excess absorption of water during transurethral prostaticectomy may also produce this syndrome.

If the degree of hyponatremia is mild, the treatment is simply water restriction. If hyponatremia is severe, the patient may develop cerebral edema and convulsions. Emergency treatment consists of water restriction and the administration of hypertonic saline according to equation [2].

C Hypernatremia Both ECW and  $\text{Na}_g^+$  are increased, but  $\text{Na}^+$  excess is greater than water excess. This disorder is almost always iatrogenic, resulting from the administration of hypertonic saline to oliguric patients.

### Disorders of Water & Sodium With Abnormal Distribution of Body Water.

In addition to changes in TBW volume, problems of abnormal distribution arise in the following common conditions: peritonitis, bowel obstruction, burns, venous obstruction, and lymphatic obstruction. Unless there is some associated abnormality in osmotic regulation, these disorders stem from a redistribution of ECW, and the ratio of  $\text{Na}^+$  to water is normal. Iso-osmotic retention of salt and water provides the volume necessary to replenish the regions from which ECW is translocated.

**A Burns** Marked edema fluid accumulates under burned skin during the first 3-4 hours after injury. Therapy based on the Evans formula relates fluid requirements to body weight and the percentage of body surface which has sustained second and third degree burns. The diagram at right can be used in estimating the percentage of body surface involved. For purposes of therapy, burns covering 50% or more of body surface are calculated as 50% each. Colloid, electrolytes, and additional water requirements are calculated according to the Evans formula as follows:

First 24 hours -

Colloid = 1 ml plasma  $\times$  % burn  $\times$  body wt in Kg

Electrolyte = 1 ml Ringer's lactate  $\times$  % burns  $\times$  body wt in Kg

Water = 2000 ml 5% dextrose in water

Second 24 hours -

Colloid =  $\frac{1}{2}$  above ration

Electrolyte =  $\frac{1}{2}$  above ration

Water = 2000 ml 5% dextrose in water

This formula is designed to provide sufficient salt, water, and protein to cover the needs arising from the burn edema, insensible losses and urine losses. In addition, 1-3

units of whole blood may be needed in extensive third degree burns because of thermal destruction of red cells. The adequacy of therapy is gauged by the PVC, the hourly urine volume (15-50 ml./hour), and clinical evaluation of circulation according to pulse rate, BP, and cyanosis.

If the patient is seen several hours after injury and is in shock, the plasma deficit may be estimated from the following equation, in which the PCV is expressed as a decimal

[4]

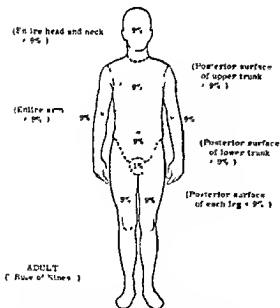
$$\text{Plasma (in L)} = \left[ \frac{\text{PCV} - 0.45}{0.55 \times \text{PCV}} \right] (0.045 \times \text{wt. in Kg.})^*$$

It is essential that the necessary amounts of plasma be administered rapidly in order to restore circulation as soon as possible.

**B Peritonitis** Acute exudation of protein-rich peritoneal fluid may rapidly cause sufficient reduction of plasma and ECW volume to result in tachycardia and hypotension. Less than 3 L. of peritoneal fluid, which may not be readily detected on examination of the abdomen, can cause this phenomenon. In patients with acute peritonitis and hypovolemic shock, the plasma deficit is determined from equation [4]. This calculation may lead to underestimation of the actual plasma loss because of the tendency of these patients to develop anemia.

**C. Bowel Obstruction** Multiple distended loops of bowel may contain 2 L. or more of fluid. The volume deficit is estimated from the formula for isotonic  $\text{Na}^+$  and water losses (equation [1]). A PCV above 50% in the presence of other clinical signs of bowel obstruction and plasma volume deficit is an indication for therapy. Early treatment will prevent shock and the complications of an abnormally high PCV.

**D Venous Obstruction** Localized edema forms distal to the obstruction because of increased filtration across capillaries into the ISW. Occasionally with obstruction of a large vessel, e.g., the inferior vena cava, marked edema in the lower portions of the body may coexist with signs of dehydration in the upper half of the body. Ordinarily patients with venous obstruction compensate by iso-osmotic retention of ingested  $\text{Na}^+$  and water. If the patient is too ill to take adequate foods and fluids, and acute obstruction has occurred, the magnitude of isotonic  $\text{Na}^+$  and water sequestration is best judged from the PCV (equation [1])



Estimation of Body Surface Area in Burns.  
(Reproduced, with permission, from  
John L. Wilson and Joseph J. McDonald,  
Handbook of Surgery. Lange, 1960.)

\*See equation 1, p. 42.

**E Lymphatic Obstruction** Lymphatic obstruction may lead to severe edema, high in protein content, distal to the area of obstruction. This is a chronic, progressive disorder which ordinarily does not produce acute fluid and electrolyte abnormalities.

## DISORDERS OF POTASSIUM METABOLISM

Disorders of  $K^+$  metabolism can be classified as follows (1)  $K^+$  depletion, (2) abnormal distribution of  $K^+$ , and (3) a combination of  $K^+$  depletion and abnormal  $K^+$  distribution. In contrast to disorders of  $Na^+$  metabolism where an excessive body content of  $Na^+$  is found in many diseases such as cardiac and hepatic diseases, there are no diseases that lead to true excess in body  $K^+$  content.

Disorders of  $K^+$  metabolism may result from defective regulation of  $K^+$  distribution, defective renal handling of  $K^+$  and extrarenal losses of  $K^+$ , or combinations of these disturbances. For a discussion of the physiologic mechanisms controlling  $K^+$  metabolism, see p. 18.

### Potassium Depletion.

A differentiation must be made between loss of protoplasm and its equivalent quantity of  $K^+$  and true  $K^+$  depletion. Any catabolic state such as might be induced by trauma, burns, major surgery, or sepsis leads to widespread cell damage or cell atrophy and liberation of the intracellular contents. The tissue is primarily affected by the catabolic response is skeletal muscle. With destruction of skeletal muscle nitrogen and potassium are liberated in a ratio of 3 Gm. nitrogen to 1 mEq. potassium. With a moderate catabolic reaction, about 10 Gm. of nitrogen and 30 mEq. of potassium are liberated per day. A severe catabolic state might liberate up to 30 Gm. of nitrogen per day and 90 mEq. of potassium. Potassium derived from catabolized tissue will be excreted in the urine and lost from the body but does not represent true  $K^+$  depletion resulting in metabolic abnormalities and does not require replacement therapy. However, in many instances of acute catabolism  $K^+$  is lost somewhat in excess of a 3:1 ratio to nitrogen, probably because of the associated increase in glucocorticoid and aldosterone secretion. This can lead to true  $K^+$  depletion and requires replacement therapy. Consequently some  $K^+$  administration is desirable when signs of  $K^+$  depletion are present, e.g., hypokalemia, metabolic alkalosis, weakness, hyporeflexia, and ECG abnormalities, either singly or in combination.

**A. Potassium Depletion in Simple Starvation** Patients maintained on potassium-free feedings may develop sizable cumulative losses of  $K^+$ . If there is no stress reaction or  $Na^+$  administration, relatively little alkalosis develops, but if a stress reaction is present and  $Na^+$  is administered the losses of  $K^+$  may be associated with the development of marked alkalosis. In potassium depletion due to inadequate intake and without alkalosis the  $K_s^+$  usually remains in the normal range until the total deficit is 3-5 mEq./Kg. Consequently, manifest hypokalemia in this setting implies that the total  $K^+$  deficit to be replaced is 3-5 mEq./Kg. or more.

**B Potassium Depletion in Alkalotic Disorders** These disorders often lead to severe hypokalemia, due both to an abnormality of  $K^+$  distribution and  $K^+$  depletion. Hypokalemia occurs early and may be present with a loss of as little as 1-2 mEq./Kg. Extreme  $K^+$  depletion develops in prolonged metabolic alkalosis, with the major route of loss usually being renal due to inappropriate excessive  $K^+$  secretion (see p. 19). Therapy often requires the administration of large amounts of  $K^+$  because of the magnitude of depletion and because large renal losses continue early in therapy until the alkalosis is corrected. For a more detailed discussion of  $K^+$  administration and associated water and electrolyte therapy in potassium depletion and alkalosis, see the section on acid-base disorders.

**C Potassium Depletion in the Acidotic Disorders** Potassium depletion of considerable magnitude frequently develops during the pathogenesis of metabolic acidosis for a variety of reasons. In diabetic acidosis dehydration and increased aldosterone secretion may lead to  $K^+$  loss in the urine. Metabolic acidosis resulting from the loss of alkaline and high  $K^+$  content, biliary, pancreatic or lower bowel secretions leads to  $K^+$  depletion. In renal tubular acidosis  $K^+$  wasting is frequently an associated renal defect.

Potassium depletion in the presence of metabolic acidosis is nearly always associated with a normal or even markedly elevated  $K_s^+$  because of the abnormality in distribution induced by acidosis. The initial treatment in such situations must be directed toward correction of abnormalities in hydration,  $Na_s^+$ , and the acidosis. Potassium repletion cannot be undertaken until the acidosis is substantially corrected and the  $K_s^+$  restored to normal. Since a period of rebound respiratory alkalosis characteristically occurs during the recovery from metabolic acidosis, it is important to

correct any potassium depletion present after the initial correction of the severe acidosis in order to avoid subsequent hypokalemia. This problem is particularly prominent during the recovery phase of diabetic acidosis. For a more detailed discussion of  $K^+$  administration and the overall management of the acidotic disorders, see the section on acid-base disorders.

**D Potassium Depletion in the Hypoosmotic (or Hyponatremic) Disorders** In many chronic illnesses such as tuberculosis and carcinoma-tosis and in severe chronic cardiac failure, cirrhosis, and nephrosis potassium depletion is usually found in association with a normal or mildly elevated  $K_2^+$  (A low  $K_2^+$  is occasionally found). Among the factors which operate to produce  $K^+$  depletion in these patients are high aldosterone levels and  $K^+$  losses in the urine induced by diuretic agents. The primary manifestation of potassium depletion in these conditions may be hyponatremia due to the loss of intracellular cation (see p. 14). For a detailed discussion of the role of  $K^+$  administration in these disorders, see pp. 27 and 29.

**E Potassium Depletion Nephropathy** This refers to a renal lesion induced by prolonged and severe potassium depletion. It is characterized by a decreased glomerular filtration rate with azotemia, isosthenuria, and hypokalemia. The magnitude of  $K^+$  depletion may exceed 10 mEq/Kg. Adequate replacement of  $K^+$  will restore the filtration rate in 1-2 weeks and in most cases gradually corrects the defect in the formation of a concentrated urine over a period of several weeks.

**F Potassium Depletion and Cardiotoxicity** In general the cardiac manifestations of potassium depletion are correlated with the  $K_2^+$  as outlined on p. 34. However, in some instances these ECG abnormalities appear with potassium depletion before manifest hypokalemia. This is particularly true in digitalized patients where digitalis toxicity may be induced by relatively mild degrees of  $K^+$  depletion and a sudden lowering of the  $K_2^+$  short of true hypokalemia.

**G. Potassium Depletion and Neuromuscular Toxicity** The neuromuscular manifestations of  $K^+$  depletion and hypokalemia are extremely variable and include weakness, hyporeflexia, paralysis, numbness, and paresthesias. Occasionally, the neuromuscular defects may be masked by the hyperirritability and even frank tetany owing to an associated alkalosis.

### Abnormal Distribution of Potassium.

In most instances abnormality of  $K^+$  distribution is associated with  $K^+$  depletion, as discussed above. In acute renal failure hyperkalemia due to abnormal distribution is frequently present as an isolated abnormality of  $K^+$  metabolism. The clinical management of this problem is discussed on p. 34. In a rapidly developing metabolic alkalosis or acute severe respiratory alkalosis, hypokalemia may develop with minimal  $K^+$  depletion as discussed above.

## ACID-BASE DISORDERS

Evaluation and treatment of acid-base disorders is based upon classification into 4 categories: respiratory acidosis, metabolic acidosis, respiratory alkalosis, and metabolic alkalosis. Two or more disturbances may exist simultaneously, volume and osmolarity abnormalities due to disorders of water,  $Na^+$ , and  $K^+$  are often also present.

### 1. RESPIRATORY ACIDOSIS

#### Pathophysiology.

The basic defect in respiratory acidosis is inadequate pulmonary excretion of  $CO_2$ , which leads to an increase in  $pCO_2$  (i.e., an increase in  $H_2CO_3$ ), a decrease in the ratio of  $NaHCO_3$  to  $H_2CO_3$ , and consequently a fall in blood pH. Renal compensation is achieved by preferential reabsorption of  $HCO_3^-$ , which increases plasma  $HCO_3^-$  concentration and restores the  $NaHCO_3/H_2CO_3$  ratio toward normal. The  $Na_2^+$  is usually not affected, the  $K_2^+$  is slightly elevated or unchanged, and the  $Cl_2^-$  usually falls. If the kidneys cannot compensate (e.g., in early acute respiratory failure or with coexisting renal failure), the  $CO_2$  content (i.e., plasma  $HCO_3^-$ ) may not be elevated and the fall in pH will consequently be greater.

Ordinarily no abnormality in the volume or osmolarity of the body water is found unless congestive heart failure is also present.

#### Etiology.

Respiratory acidosis may be found in any disorder associated with inadequate ventilation: pulmonary emphysema, pulmonary fibrosis and other diffuse pulmonary disease, poliomyelitis with paralysis of the muscles of respiration, acute airway obstruction, hypoventilation dur-

ing surgery, and depression of the respiratory center by drug toxicity or CNS disease

#### Differential Diagnosis.

It is important not to confuse respiratory acidosis and metabolic alkalosis, in which the serum  $\text{CO}_2$  content is also elevated, the latter is usually accompanied by a decrease in  $\text{K}_s^+$ . In patients with both pulmonary disease and a possible cause of metabolic alkalosis (e.g., peptic ulcer with vomiting), blood pH may be the only method of diagnosis

#### Treatment

Treatment consists of improving ventilation and pulmonary  $\text{CO}_2$  excretion. Congestive heart failure, if present, is managed by conventional measures.

## 2 METABOLIC ACIDOSIS

#### Pathophysiology.

The basic defect in metabolic acidosis is a loss of  $\text{NaHCO}_3$  buffer salt which results in a decrease in the  $\text{NaHCO}_3/\text{H}_2\text{CO}_3$  ratio and consequently a fall in pH. The appropriate pulmonary response is increased excretion of  $\text{CO}_2$  ( $\text{H}_2\text{CO}_3$ ), a decrease in  $\text{pCO}_2$ , and hence restoration of the  $\text{NaHCO}_3/\text{H}_2\text{CO}_3$  ratio toward normal.

The serum  $\text{CO}_2$  content in metabolic acidosis is low. The  $\text{Na}_s^+$  is determined by the associated changes in  $\text{Na}^+$ ,  $\text{K}^+$  and water balance. Ordinarily the  $\text{Cl}_s^-$  is normal or low, but it may be elevated in patients with renal tubular acidosis, ureterosigmoidostomy, or in any state characterized by hyperosmolality. In the latter situation the  $\text{Na}_s^+$  is also usually high. Characteristically the  $\text{K}_s^+$  is moderately to severely elevated in metabolic acidosis. In a few cases, however, sufficient  $\text{K}^+$  may be lost in the urine or gastrointestinal secretions so that the  $\text{K}_s^+$  is normal or even low, despite the presence of advanced acidosis. The highest values of  $\text{K}_s^+$  occur in patients with renal failure. The serum  $\text{HPO}_4^-$  is elevated when there is reduction in glomerular filtration rate.

#### Etiology.

Four common pathways may lead to metabolic acidosis:

A Excessive Excretion of  $\text{NaHCO}_3$ . The loss of biliary, pancreatic, or lower bowel secretions via fistulas or because of diarrhea results in varying degrees of  $\text{HCO}_3^-$  depletion. An impaired ability of the kidney to reabsorb

$\text{NaHCO}_3$  may be either congenital or acquired (e.g., chronic pyelonephritis) and leads to renal tubular acidosis. In patients with a ureterosigmoidostomy,  $\text{Cl}^-$  reabsorption and  $\text{HCO}_3^-$  secretion by the colonic membrane often produces moderate to severe metabolic acidosis.

#### B Excessive Production of Metabolic Acids

In patients with uncontrolled diabetes mellitus, the overproduction of organic acids leads to a fall in plasma  $\text{HCO}_3^-$ .

#### C Failure to Excrete Metabolic Acids

In renal failure, particularly where the glomerular filtration rate is markedly reduced, uremia and metabolic acidosis result. The latter because of a failure to clear the plasma of the acids released by metabolic degradation of proteins.

#### D Excessive Ingestion of Acid-forming Substances

Acidosis medicamentosa may result from ingestion of large quantities of  $\text{NH}_4\text{Cl}$ ,  $\text{FeSO}_4$ , methyl alcohol, or a variety of other acids or precursors of acids.

#### Differential Diagnosis

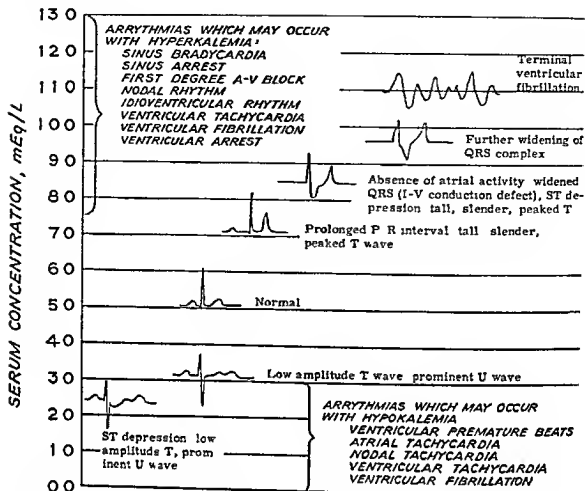
At the bedside it is difficult to detect the compensatory increase in ventilation unless the plasma  $\text{HCO}_3^-$  is  $< 15 \text{ mEq/L}$ . Consequently, if hyperventilation is obvious when the plasma  $\text{HCO}_3^-$  is  $> 15 \text{ mEq/L}$ , primary respiratory alkalosis should be suspected.

It is important not to confuse metabolic acidosis with respiratory alkalosis. Each of these acid-base disturbances may appear in similar clinical settings. A blood pH may be necessary for diagnosis.

#### Treatment

The volume and electrolyte content of replacement solutions not only must correct the initial defects in the volume, osmolality, and acid-base composition of the ECW, but must replace continuing insensible, urinary, and other losses as well. Estimates of fluid and electrolyte replacement must be revised daily according to the response of the patient.

A Volume and Osmolality. Dehydration with or without disturbances in  $\text{Na}_s^+$  is common in patients with gastrointestinal losses, renal disease, or diabetic acidosis. The deficits in ECW volume and osmolality may be estimated from equations [1], [2], and [3]. In addition, an accurate history of changes in body weight, accurate records of fluid losses, and physical examination will help determine the magnitude and character of ECW abnormalities.



Rough Correlation Between  $K^+$  & the ECG (In hyperkalemia the cardiotoxicity at a given  $K^+$  becomes more marked by a decrease of  $Na^+$ . Thus with severe hyponatremia far-advanced cardiotoxicity may be seen with a  $K^+$  of 7.5 mg/L)

B  $HCO_3^-$   $Na^+$   $Cl^-$   $NaHCO_3$  buffer salt is replaced by administration of  $NaHCO_3$  or  $Na$  lactate. The total deficit in  $HCO_3^-$  may be approximated as follows

[5]

mEq  $HCO_3^-$  deficit -

$(28 - \text{plasma } CO_2) (0.4 \times \text{wt in Kg})$

Only two-thirds of the total  $HCO_3^-$  deficit should be replaced as  $NaHCO_3$  or  $Na$  lactate during the first 24-48 hours. A rebound respiratory alkalosis commonly occurs during recovery from metabolic acidosis and this will be greater in intensity if the serum  $HCO_3^-$  is restored fully early in therapy.

Any remaining  $Na^+$  deficit is replaced as  $NaCl$

Even in the absence of dehydration or  $Na^+$  depletion as in acute renal failure it may be necessary to administer hypertonic  $Na$  lactate to correct severe metabolic acidosis (i.e.,  $HCO_3^- < 12 \text{ mEq/L}$ ) even though this may result in an excess content of  $Na^+$  in the body

C Potassium Hyperkalemia is a frequent complication of metabolic acidosis, especially when there is extensive tissue damage. In some instances the cardiotoxic effects of hyperkalemia threaten the survival of the patient (see above). The most useful techniques for controlling or lowering  $K^+$  are as follows: (1) Elimination of all dietary  $K^+$ , (2) debridement of necrotic tissue and control of infections, (3) rehydration and control of acidosis with  $Na$  lactate or  $NaHCO_3$ , (4) use of sodium-loaded cation exchange resins. Sodium polystyrene

sulfonate (Kayexalate®), 40-50 Gm /day in 4 divided doses may be used (It is assumed that 1 mEq  $K^+$  is removed/Gm of resin and that 3 mEq  $Na^+$  is supplied to the patient.) This dosage will often return the  $K_g^+$  to normal in 1-2 days. A maintenance dose of 20 Gm / day may be used to control the  $K_g^+$  in acute renal failure. The resin requires 3-4 ml of water/Gm of resin for solution. It is important for the patient to have a daily bowel movement in order to prevent a resin impaction. This may necessitate the simultaneous administration of a mild cathartic. When oral medication is not feasible, the resin may be given every 6 hours as an enema of 20-40 Gm of resin in 200 ml of water or 200 ml of 25% sorbitol, which acts as an osmotic cathartic.

The following emergency measures may control life-threatening cardiotoxicity for a few hours: (1) Glucose solution, 25% 300 ml, containing 1 unit of crystalline zinc insulin/Gm of glucose, administered I V over a period of one-half hour. (2) Calcium gluconate, 10%, 20-50 ml I V slowly (Note: Calcium gluconate should be used cautiously in digitalized patients.) (3) Molar Na lactate, 150 ml, or 5% NaCl, 200 ml, I V. Hypertonic saline solution is the most rapid and effective therapy in far-advanced cardiotoxicity. However, it carries the risk of causing acute pulmonary edema and produces effects lasting only 1-2 hours, and its use should therefore be reserved for severe emergencies. When hypotatremia is present, on the other hand, hypertonic saline solution may produce a more lasting effect and is the treatment of choice. Na lactate is more apt to be effective than NaCl.

In patients with acute renal failure all of these methods may fail to control the  $K_g^+$ , and hemodialysis or peritoneal dialysis will be required.

Severe total body  $K^+$  depletion may be masked during acidosis by a normal or elevated  $K_g^+$ . As the acidosis is corrected, this depletion may appear as hypokalemia. In patients with diabetic acidosis, gastrointestinal losses, renal tubular acidosis, ureterosigmoidostomy, or chronic ingestion of  $NH_4Cl$ , depletion is usually of considerable magnitude, 2-5 mEq /Kg body weight. The administration of  $K^+$  is hazardous, however, when  $K_g^+$  is elevated or when marked oliguria exists. Once acidosis is partially corrected, the urine volume is  $>20$  ml./hour (except in patients with known acute renal failure) and  $K_g^+$  and ECG are normal, replacement of the estimated  $K^+$  depletion may be started. Except in unusual circumstances  $K^+$  should not be given I V. In a concentration greater than 50 mEq /L. Ordinarily I V. administration is needed only in patients with

diabetic acidosis or acute gastrointestinal losses. In these cases 100-150 mEq /day of  $K^+$  will prove adequate and safe except when  $K^+$  continues to be lost at a brisk rate.

Note: Do not overtreat with  $NaHCO_3$  and Na lactate. As noted above, there is commonly a period of respiratory alkalosis during the recovery from metabolic acidosis. Excessive administration of buffer salts will exaggerate the rebound alkalosis and hence intensify hypokalemia when  $K^+$  depletion is present.

### 3 RESPIRATORY ALKALOSIS

#### Pathophysiology.

The basic defect in patients with respiratory alkalosis is excessive pulmonary excretion of  $CO_2$ , a resultant decrease of  $pCO_2$  (decreased  $H_2CO_3$ ), an increase in the ratio of  $NaHCO_3$  to  $H_2CO_3$ , and consequently a rise in blood pH. Compensation is achieved by 2 mechanisms: (1) Suppression of renal tubular reabsorption of  $NaHCO_3$ , which leads to an increased urinary excretion of  $NaHCO_3$ , and (2) increased metabolic production of organic acids. A considerable elevation of pH often occurs early in respiratory alkalosis. This is due to the fact that the renal mechanism is not immediately effective.

Ordinarily in respiratory alkalosis the  $Na_g^+$  is normal,  $K_g^+$  normal or decreased,  $Cl_g^+$  normal or increased, and the plasma  $CO_2$  content decreased.

Respiratory alkalosis produces a characteristic syndrome of neuromuscular irritability manifested by hyperreflexia, a positive Chvostek sign, muscular twitching, and at times a generalized convulsion. It should be strongly suspected in any of the clinical conditions listed below and when hyperventilation seems out of proportion to the fall in  $CO_2$  content, in renal failure it may coexist with metabolic acidosis. At times the only certain means of diagnosis is by simultaneous measurement of plasma  $CO_2$  content and arterial pH. The urine pH is often not of diagnostic help, although if the urine is alkaline when plasma  $CO_2$  is decreased (and if there is no urea-splitting bacterial urinary tract infection), respiratory alkalosis should be suspected. The urine may be mildly or markedly acid when there is a superimposed  $K^+$  deficiency, dehydration, or in far-advanced respiratory alkalosis (in which there may be an excessive compensatory production of metabolic acid).

### Etiology

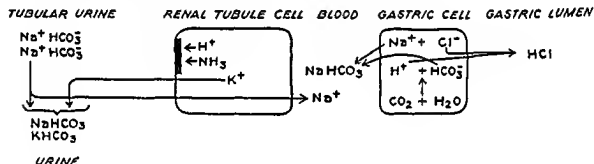
The commonest causes of respiratory alkalosis are anxiety states, cerebral diseases such as thrombosis, hemorrhage, or head injury, gram-negative rod septicemias and other acute infections, hepatic coma, pulmonary alveolar capillary block, and salicylate poisoning (although late in the course of salicylate poisoning the findings may be those of metabolic acidosis).

### Differential Diagnosis

It is vital not to confuse respiratory alkalosis and metabolic acidosis. The erroneous administration of alkalinizing salts (e.g.  $\text{NaHCO}_3$  and  $\text{Na}$  lactate) will intensify the alkalosis and may prove fatal.

### Treatment

Anxiety-induced respiratory alkalosis is best treated by sedation and rebreathing into a paper bag. In more prolonged and severe respiratory alkalosis treatment of the underlying disease is the most effective therapy.



When respiratory alkalosis continues for several days, significant  $\text{K}^+$  depletion and hypokalemia may occur. This should be treated by the administration of about 1 mEq of  $\text{K}^+/\text{Kg}$  body weight/day.

Breathing 5%  $\text{CO}_2$  may be tried, but it often accentuates hyperventilation, especially in patients with hepatic coma.

## 4 METABOLIC ALKALOSIS

### Pathophysiology.

Metabolic alkalosis is characterized by an increase in plasma  $\text{HCO}_3^-$ , a resultant increase in the  $\text{NaHCO}_3/\text{H}_2\text{CO}_3$  ratio, and consequently a rise in pH. Hypoventilation, which tends to raise the  $\text{pCO}_2$  ( $\text{H}_2\text{CO}_3$ ), provides limited compensation. Usually both the rate and the mag-

nitude of rise in pH are less in patients with metabolic alkalosis than in those with respiratory alkalosis. As a result, cerebral disturbances and symptoms of tetany are often less prominent in metabolic alkalosis.

The  $\text{Na}^+$  may be elevated if sizable losses of sweat and insensible perspiration have occurred, or it may be depressed if water has been administered. Serum  $\text{K}^+$  concentration is usually decreased, often to very low levels. The  $\text{Cl}^-$  is usually low, and the plasma  $\text{CO}_2$  content is high.

### Etiology.

Metabolic alkalosis most commonly occurs as a result of any of the following conditions:

**A. Loss of Gastric Juices.** The loss of gastric  $\text{HCl}$  by suction or vomiting causes renal suppression of  $\text{H}^+$  and  $\text{NH}_3$  secretion. As a result,  $\text{NaHCO}_3$  and  $\text{KHCO}_3$  are excreted in the urine (see below). With continued isotonic losses of water,  $\text{Na}^+$  and  $\text{K}^+$ , however, this renal mechanism will fail.

The need to conserve  $\text{Na}^+$  will activate renal mechanism 1 (p. 17) in which  $\text{Na}^+$  is exchanged for  $\text{H}^+$  in the distal tubule. Because  $\text{Na}^+$  is reabsorbed with  $\text{HCO}_3^-$ , the plasma  $\text{HCO}_3^-$  will rise, as loss of gastric  $\text{HCl}$  continues. An uncompensated metabolic alkalosis is the result.

**B. Use of Diuretics.** Mercurial diuretics produce an isotonic urinary excretion of  $\text{NaCl}$  and water.  $\text{K}^+$  excretion is increased in varying degrees. The thiazide diuretics also produce a mild to moderate metabolic alkalosis, since  $\text{K}^+$  depletion is usually greater than with the use of mercurial diuretics.

**C. Hyperadrenocorticism.** Prolonged excessive action of aldosterone, cortisone, and hydrocortisone causes  $\text{K}^+$  depletion,  $\text{K}^+$  depletion nephropathy, and metabolic alkalosis, generally without much change in the volume.



or osmolality of the body fluids (except in patients with primary aldosteronism, who will have a moderately elevated  $\text{Na}^+$ ).

**D. Renal Disease.** In rare instances  $\text{K}^+$  wasting and metabolic alkalosis are a major feature of chronic pyelonephritis.

**E. Chronic Diarrhea and Excessive Use of Cathartics.** The  $\text{K}^+$  deficits in these patients are frequently large (3-10 mEq./Kg.) The alkalosis, however, is usually mild, probably because of the loss of  $\text{NaHCO}_3$  in the stools. Further, when  $\text{K}^+$  depletion becomes marked, urinary losses of  $\text{K}^+$  decrease (in contrast to steroid-induced  $\text{K}^+$  depletion).

**F.  $\text{NaHCO}_3$  Ingestion.** Chronic ingestion of  $\text{NaHCO}_3$  usually is compensated for fairly well by the kidneys if there is no  $\text{Na}^+$  or water depletion. However, if the use of alkalies is prolonged, a sizable  $\text{K}^+$  deficit may develop, renal compensation will be impaired, and marked alkalosis will result. Ingestion of  $\text{NaHCO}_3$  and loss of gastric  $\text{HCl}$  by intermittent vomiting (as in some peptic ulcer patients) will also lead to severe alkalosis.

### Differential Diagnosis.

Metabolic alkalosis may be confused with respiratory acidosis. It is important to make this differentiation since metabolic alkalosis may be due to  $\text{K}^+$  loss and  $\text{K}^+$  must be given.

### Treatment.

In some cases, correction of the underlying disease and simple  $\text{K}^+$  replacement are sufficient to correct the metabolic alkalosis. In other cases, replacement therapy must be calculated carefully and administered over several days.

**A. Loss of Gastric Juices.** Isotonic saline requirements are calculated from equation [1] or, if necessary, according to changes in body weight. The  $\text{K}^+$  deficit will usually be 3-10 mEq./Kg. The  $\text{Na}^+$  and water deficit should be corrected within 12-24 hours (see equations [2] and [3]), whereas correction of the  $\text{K}^+$  deficit will require about 48 hours. Full correction of the alkalosis should be achieved in 48-72 hours. Response to therapy is based on daily PCV, serum electrolyte determinations, and body weight. In addition to replacing deficits, sufficient  $\text{Na}^+$ ,  $\text{K}^+$ , and water must be provided to cover continuing daily losses. Gastric losses can be replaced volumetrically with 155 mEq./L. of  $\text{NaCl}$  and 40 mEq./L. of  $\text{KCl}$ . Insensible and urinary losses require 2-3 L. of water/day for replacement. This should be given as 5 or 10% glucose.

Although  $\text{KCl}$  and the replacement of the deficit in ECW volume are usually adequate to correct the alkalosis, occasionally it may be necessary to administer 0.9%  $\text{NH}_4\text{Cl}$  because of the loss of large quantities of highly acid gastric secretions. The amount to be administered depends upon the ECW  $\text{Cl}^-$  deficit.

[6]

$$\text{mEq } \text{Cl}^- \text{ (as } \text{NH}_4\text{Cl}) =$$

$$(104 - \text{Cl}_g)(0.2 \times \text{wt. in Kg.})$$

One-half the calculated volume is administered, the serum  $\text{HCO}_3^-$  is re-checked, and the necessity for further therapy is determined.

**Note:** The volume of gastric secretion may increase sharply just before surgery, and this should be watched for to make certain that replacement therapy is adequate to prevent recurrence of alkalosis. In patients with hepatocellular disease  $\text{NH}_4\text{Cl}$  is contraindicated, but arginine hydrochloride may be used.

**B. Use of Diuretics.** Simple replacement of  $\text{K}^+$  is often effective in reversing the alkalosis and restoring sensitivity to mercurial diuretics. The usual oral dosage is 1-2 mEq./Kg./day. If  $\text{K}^+$  therapy is ineffective, or if it is not feasible because of poor tolerance,  $\text{NH}_4\text{Cl}$ , 4-8 Gm. daily for 4 days, may prove effective.

**C. Hyperadrenocorticism:** Treatment of the underlying condition (e.g., removal of an adrenal tumor) and replacement of  $\text{K}^+$  are usually effective in reversing metabolic alkalosis. In contrast to patients with  $\text{K}^+$  depletion due to chronic diarrhea or renal disease, steroid-induced  $\text{K}^+$  loss continues at the same high level as long as excessive steroids are present.

**D. Renal Disease.** In chronic pyelonephritis with  $\text{K}^+$  wasting, the metabolic alkalosis can be readily corrected by adequate  $\text{K}^+$  repletion.

**E. Chronic Diarrhea and Excessive Use of Cathartics.** Therapy consists primarily of correcting the diarrhea or withholding cathartics.  $\text{K}^+$  repletion is effected by daily oral administration of 1-2 mEq. of  $\text{K}^+$ /Kg. for a period of several days.

**F.  $\text{NaHCO}_3$  Ingestion.** Treatment consists of stopping  $\text{NaHCO}_3$  ingestion and the administration of 1-2 mEq. of  $\text{K}^+$ /Kg. daily for several days.

## ABNORMALITIES IN METABOLISM OF OTHER CATIONS

### ABNORMALITIES IN MAGNESIUM METABOLISM

Evidence indicates that  $Mg^{++}$  is essential for many anabolic and catabolic enzyme systems but very little clinical information is available regarding abnormalities in  $Mg^{++}$  metabolism. This may be due to the difficulty of measuring  $Mg^{++}$  in body fluids accurately.

$Mg^{++}$  is present in low concentrations in the ECV and in considerably higher concentrations in the ICV. Bone contains about 75% of the total body  $Mg^{++}$ . The normal  $Mg^{++}$  varies from 1.8-2.5 mEq/L, a fraction of which is protein-bound.

Administration of large amounts of  $Mg^{++}$  will produce general anesthesia, skeletal muscle paralysis and cardiotoxicity. The cardiac effects are similar to those found in hyperkalemia and consist of elevated T waves, atrioventricular and ventricular conduction defects and cardiac arrest.

Most clinical studies of spontaneous disorders in  $Mg^{++}$  metabolism have attempted to correlate symptoms with changes in serum levels.

Hypomagnesemia has been reported in patients with prolonged loss of gastrointestinal fluids, cirrhosis, delirium tremens, hyperparathyroidism after recovery from diabetic acidosis, during the diuretic phase of acute renal failure, and in primary aldosteronism. Although balance studies have generally not been done, it has usually been suggested that these are  $Mg^{++}$  deficiency states. Latent tetany (positive Chvostek's and Trousseau's signs and muscular twitching enhanced by auditory or mechanical stimuli) and frank tetany (facial muscle spasms, carpal pedal spasms, athetoid and choreiform movements and convulsions) have been correlated with low  $Mg^{++}$  levels. There is considerable doubt about whether alterations in sensorium (confusion, semicomatose and recurrent delirium tremens) can be correlated with hypomagnesemia. Cardiac arrhythmias have not definitely been shown to occur, but cardiotoxicity similar to that seen with hypokalemia has been correlated with hypomagnesemia.

If symptomatic hypomagnesemia is suspected the recommended therapy is 1 M administration of 2-4 ml of 50%  $MgSO_4$  solution every 6 hours (64-128 mEq  $Mg^{++}$ /24 hours) for 24-72 hours or until symptoms are re-

lieved. Patients with prolonged loss of gastrointestinal fluids should probably receive 10-20 mEq of  $Mg^{++}$ /day.

Hypermagnesemia has been reported in patients with diabetic acidosis, acute renal failure, and occasionally in chronic renal failure. No clinical manifestations of hypermagnesemia, however, have been conclusively demonstrated in these disorders.

### ABNORMALITIES IN CALCIUM & PHOSPHATE METABOLISM

Many of the abnormalities in  $Ca^{++}$  and  $HPO_4^{--}$  metabolism are the result of parathyroid or bone disease and will not be discussed here. Other abnormalities in  $Ca^{++}$  and  $PO_4^{--}$  metabolism are mostly associated with disturbances in acid-base metabolism and renal disease.

Phosphate retention and elevation of serum  $HPO_4^{--}$  is characteristically present in severe renal failure in association with metabolic acidosis when the glomerular filtration rate falls to less than 30 ml/minute. When hyperphosphatemia exists, the  $Ca^{++}$  often reciprocally falls. Hypocalcemia may, in part, be responsible for the muscular twitching, muscle cramps and convulsions in uremia.

Acidosis tends to raise the convulsive threshold in hyperphosphatemic patients, whereas alkalosis lowers it. Consequently, excessive administration of Na lactate or  $HCO_3^-$  is to be avoided - or these agents should be administered with  $Ca^{++}$  - if there is evidence of increasing neuromuscular irritability. Metabolic acidosis with a plasma  $HCO_3^-$  content > 20 mEq/L ordinarily does not require the administration of alkalies.

In chronic renal failure, phosphate absorption from the gut may be retarded by the administration of aluminum hydroxide gel, 30-50 ml (or 4-6 Gm) after meals and at bedtime. The oral administration of calcium gluconate 1 Gm tid, may be helpful in minimizing the symptoms of hypocalcemia in chronic renal failure.

## MAINTENANCE THERAPY

In addition to correction of the initial fluid and electrolyte disorder, replacement therapy must also provide for continuing losses. Main-

tenance therapy is calculated from average daily basal losses of electrolyte and fluid, but it must be adjusted according to variations in minimum urine volume, metabolic water production, and special losses such as occur with fever or gastrointestinal drainage

#### Daily Average Basal Losses.

A 70 Kg man in the resting state will lose body water and electrolytes in the following amounts per 24 hours

Route	Water (ml)	mEq/L		
		Na <sup>+</sup>	K <sup>+</sup>	Cl <sup>-</sup>
Insensible (skin, lungs)	800 (12 ml/Kg)	0	0	0
Urine	1200	70	30	75
Stool	200	5	10	5
Total	2200	75	40	80

#### Average Maintenance Requirements

Basal losses may be replaced as follows

Solution	Water (ml.)	mEq			Glucose (Gm)
		Na <sup>+</sup>	K <sup>+</sup>	Cl <sup>-</sup>	
1 L. 5% dextrose in 0.5-N saline with 20 mEq KCl	1000	77	20	97	50
1 L. 10% dextrose in water with 20 mEq KCl	1000		20	20	100
Total	2000	77	40	117	150

These are average figures and do not apply to all patients. Adjustments will have to be made according to increased losses (e.g., fever, gastrointestinal drainage, urinary solute load) or increased production (e.g., water of metabolism)

#### Daily Volume & Content of Sweat Losses

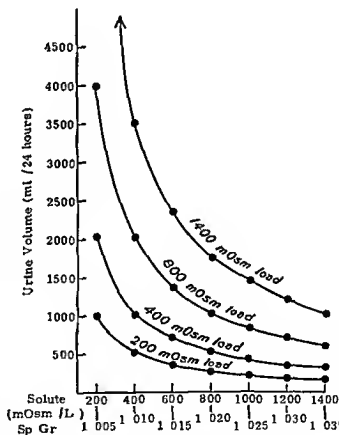
	Water (ml)	Na <sup>+</sup> (mEq/L)	Cl <sup>-</sup> (mEq/L)
38°C (101°F) or more, moderate sweating	1000-1500	50	50
Severe, constant sweating	1000-5000	30	30

#### Minimum Daily Urine Volume

The minimum 24-hour urine volume is determined by the total amount of solute presented for excretion and by the ability of the

kidney to concentrate solute. Maximum urine osmolarity (i.e., the greatest solute load that the kidney will be able to handle) is about 1400 mOsm/L.

If the concentrating ability of the kidney is impaired, the volume of urine required to handle a given solute load must be increased, conversely, the same solute load can be excreted in less volume if the kidney is able to put out a concentrated urine (see below). For example, solute excretions of 800 mOsm/day would require a urine volume of 2000 ml if the specific gravity is 1.010, whereas if the specific gravity is 1.035 about 500 ml of urine will be required.



**Total Solute Excretion & Urine Volume per Given Sp.Gr.** (Redrawn and reproduced, with permission, from John H. Bland, Clinical Recognition and Management of Disturbances of Body Fluids, Saunders, 1956)

The 24-hour urine volume and specific gravity should always be interpreted in the light of the solute load. An average diet presents 600-1200 mOsm of solute for excretion, which will consist primarily of urea (from protein catabolism) and the salts of Na<sup>+</sup> and K<sup>+</sup>.

## Parenteral Glucose &amp; Electrolyte Solutions

Solution	Electrolyte Concentration (mEq / L )						Glucose (Gm / L )
	Na <sup>+</sup>	K <sup>+</sup>	Ca <sup>++</sup>	NH <sub>4</sub> <sup>+</sup>	HCO <sub>3</sub> or Lactate	Cl	
5% glucose in water							50
10% glucose in water							100
Normal saline (0.9% NaCl)	155					155	
Half normal saline (0.45% NaCl)	77					77	
5% glucose in normal saline	155					155	50
5% glucose in 1/2 normal saline	77					77	50
10% glucose in 1/2 normal saline	77					77	100
3% saline (hypertonic saline)	515					515	
5% saline (hypertonic saline)	850					850	
Hartmann's solution (Ringer's lactate)	132	4	4		28	112	
Sixth molar Na lactate	166				166		
Sixth molar NaHCO <sub>3</sub>	166				166		
0.9% NH <sub>4</sub> Cl				170*		170	
Gastric replacement solution (Baxter)	63	17.5		70*		150	
Arginine hydrochloride 5% (R. gene <sup>®</sup> )				240*		240	
Electrolyte Solution D for duodenal replacement (Abbott)	138	12			50	100	

\*NH<sub>4</sub><sup>+</sup> is converted to H<sup>+</sup> in body mEq for mEq

## Electrolyte Concentrates

Concentrate	Supplied as	Electrolyte Content*					
		Na <sup>+</sup>	K <sup>+</sup>	NH <sub>4</sub> <sup>+</sup>	Ca <sup>++</sup>	Mg <sup>++</sup>	Cl HCO <sub>3</sub> Lactate
KCl	10 ml ampules		20				20
KMC	10 ml ampules		25		10	10	45
MgSO <sub>4</sub>	50% solution					8†	
Na lactate molar solution	40 ml ampules	40					40
NaHCO <sub>3</sub>	50 ml ampules	45					45
NH <sub>4</sub> Cl	30 ml ampules			120‡			120

\*Total mEq / ampule unless otherwise specified Note The physician should always check contents of the ampule as listed by manufacturer

†mEq / ml

‡NH<sub>4</sub><sup>+</sup> is converted to H<sup>+</sup> in the body mEq for mEq

## Oral Electrolyte Preparations

Preparation	Supplied as	Electrolyte Content*					
		Na <sup>+</sup>	K <sup>+</sup>	NH <sub>4</sub> <sup>+</sup>	Ca <sup>++</sup>	Cl	HCO <sub>3</sub>
NaCl	Salt	17				17	
NaHCO <sub>3</sub>	Salt	12					12
KCl	Salt		14			14	
K triplex <sup>®</sup>	Elixir		15 mEq / 5 ml				
K gluconate (Kaon <sup>®</sup> )	Elixir		7 mEq / 5 ml				
Ca gluconate	Salt				4.5		
Ca lactate	Salt				10		
NH <sub>4</sub> Cl (acidifying salt)	Salt			18†		18	
Kayexalate* (ion exchange resins)	Salt	1‡	‡				

\*mEq / Gm unless otherwise specified

†NH<sub>4</sub><sup>+</sup> is converted to H<sup>+</sup> in the body mEq for mEq

‡1 Gm resin removes 1 mEq K<sup>+</sup> and contributes 3 mEq Na<sup>+</sup> to patient

Since each 100 Gm of protein produces about 500 mOsm of urea for excretion, a high-protein gavage formula may yield a solute load in excess of 1200 mOsm /24 hours. Further, when urinary excretion of  $\text{NaHCO}_3$  is increased, the solute load may reach 1200-1400 mOsm /24 hours. In patients with diabetic acidosis, the osmotic diuresis produced by keto acids may exceed 3000 ml /24 hours and the solute excretion 1400 mOsm /24 hours.

The fasting patient produces about 500 mOsm of solute/24 hours. This can be reduced to about 300 mOsm by feeding 100 Gm of carbohydrate. A resting patient on a low  $\text{Na}^+$  and high carbohydrate intake (common in patients receiving parenteral fluids) may excrete only 200 mOsm of solute/24 hours. On the other hand, the fasting or carbohydrate-fed patient with intense catabolism may excrete more than 1200 mOsm /24 hours.

#### Water of Metabolism

In the basal state metabolic processes produce about 200 ml of water/24 hours. This figure is subtracted from the daily basal losses in calculating average maintenance therapy. In marked catabolic states, however, water of metabolism may amount to 800 ml /24 hours. Therefore in calculating fluid replacement in oliguric patients who are also hypercatabolic, the water of metabolism must be subtracted from estimated losses.

#### Gastrointestinal Losses

The volume and electrolyte content of losses occurring at various levels of the gastrointestinal tract are shown on p. 31.

In addition, the following facts should be kept in mind:

The total volume of secretion in the normal bowel at a given time is small (about 1-2% of body weight). The amounts listed in the table cover a 24-hour period.

Except for acid gastric juice and some diarrheal stools, the  $\text{Na}^+$  concentration is high and approaches that of the ECW. Extremely high  $\text{Na}^+$  concentrations may be present in bile and pancreatic juice.

Potassium concentration is relatively low but may be as high as 40 mEq /L or more. Bicarbonate concentration is extremely high in pancreatic juice and somewhat above that of plasma throughout the lower intestinal tract.

When gastrointestinal losses are large and prolonged, the concentration of  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  in the gastrointestinal fluid should be measured at least once to assess the losses accurately. This is essential in biliary and pancreatic losses.

## STANDARD REPLACEMENT PREPARATIONS

(See table on p. 40.)

Calculate replacement therapy for each 24-hour period and determine time of administration and flow rate accordingly. With continuing large losses the most physiologic replacement is achieved by administering the fluid continuously over the 24-hour period.

One ml contains approximately 20 drops. The maximum rate at which 1 V glucose should be given is about 15-20 Gm /hour, i.e.

#### Volume & Electrolyte Content of Gastrointestinal Fluid Losses

Secretion*	$\text{Na}^+$ (mEq /L )	$\text{K}^+$ (mEq /L )	$\text{Cl}^-$ (mEq /L )	$\text{HCO}_3^-$ (mEq /L )	Volume (ml )
Gastric juice - high in acid	20 (10-30)	10 (5-40)	120 (80-150)	0	1000-9000
Gastric juice - low in acid	80 (70-140)	15 (5-40)	90 (40-120)	5-25	1000-2500
Pancreatic juice	140 (115-180)	5 (3-8)	75 (55-95)	80 (60-110)	500-1000
Bile	148 (130-160)	5 (3-12)	100 (90-120)	35 (30-40)	300-1000
Small bowel drainage	110 (80-150)	5 (2-8)	105 (60-125)	30 (20-40)	1000-3000
Distal ileum and cecum drainage	80 (40-135)	5 (5-30)	45 (20-90)	30 (20-40)	1000-3000
Diarrheal stools	120 (20-160)	25 (10-40)	90 (30-120)	45 (30-50)	500-17 000

\*Average values/24 hours with range in parentheses

120-140 drops/minute of 5% dextrose in water or 60-70 drops/minute of 10% dextrose in water.

In cardiac patients the maximum infusion rate of hypertonic saline solution is 30 drops/minute. In salt-depleted patients for whom hypertonic saline is indicated, the rate may be as high as 80 drops/minute.

Hypodermoclysis should be used only for 5% dextrose in water solutions, it should be avoided in dehydrated patients.

The maximum infusion rate of  $K^+$  is usually 15 mEq/hour. In patients with marked  $K^+$  depletion and metabolic alkalosis rates up to 30 mEq./hour may be well tolerated.

In most instances the proper replacement solutions will be among those listed below or can be prepared from one of these solutions by adding electrolyte concentrates. For example, in metabolic alkalosis with large deficits of water,  $Na^+$ , and  $K^+$ , normal saline with 40 mEq KCl added is the solution of choice. In patients with  $Na^+$ ,  $Cl^-$ ,  $HCO_3^-$ , and water depletion, Hartmann's solution (Ringer's lactate) may be appropriate. If the metabolic acidosis is severe, half-normal saline with 70 ml of molar Na lactate/L. may be appropriate. If there is no  $Cl^-$  deficit but a large  $Na^+$  and  $HCO_3^-$  deficit, sixth-molar Na lactate may be the solution of choice.

In patients with continuing gastrointestinal losses (after the initial volume-osmolality and acid-base disorder has been corrected), normal saline supplemented with KCl is usually adequate. If renal function is impaired, precisely calculated replacement is essential. In some gastrointestinal losses (e.g., biliary and pancreatic juices) replacement must be based on the measured electrolyte content of the lost fluid.

## DERIVATIONS OF EQUATIONS

The equations described below can be applied for useful approximation of plasma or ECW deficit only when RCV remains relatively constant. Therefore, if there is a sizable gain or loss of red blood cells due to any cause or marked change in body water osmolality such as would occur with associated hypernatremia, hyponatremia, or a rapidly changing BUN, these equations cannot be used. They are most useful for approximating large short-term plasma and ECW deficits when serial hematocrits are available. When  $(PCV_1)$  is not known, an assumed normal  $(PCV_1)$  of 0.4 or 0.45 may

be successfully used in the equation in many instances.

### Equation I.

Derivation of equation relating plasma deficit to change in hematocrit when total red blood cell volume (RCV) remains constant

$$RCV_1 = RCV \text{ before plasma loss}$$

$$RCV_2 = RCV \text{ after plasma loss}$$

Now  $RCV_1$  can be expressed as

$$\frac{PCV_1}{(1 - PCV_1)} (0.045 \times \text{body wt. in Kg.})$$

assuming that the average plasma volume is 45% of body weight,

and  $RCV_2$  can be expressed as

$$\frac{PCV_2}{(1 - PCV_2)} (0.45 \times \text{body wt. in Kg.} - x)$$

where  $x$  = liters of plasma deficit.

Since we have specified that the total red blood cell volume remains constant,

$$RCV_1 = RCV_2$$

$$\frac{PCV_1}{(1 - PCV_1)} (0.045 \times \text{body wt.}) =$$

$$\frac{PCV_2}{(1 - PCV_2)} (0.045 \times \text{body wt.} - x)$$

$$x = \frac{(PCV_2 - PCV_1)}{PCV_2(1 - PCV_1)} (0.045 \times \text{body wt.})$$

### Equation II.

Derivation of equation relating ECW deficit to change in hematocrit.

Again the RCV must remain constant. It is assumed that the change in ECW is in direct proportion to the change in plasma volume with isotonic  $Na^+$  and  $H_2O$  depletion. This is not strictly true since the rising concentration of serum protein will tend to maintain plasma volume. This can be corrected by slightly overestimating ECW volume as 20% of body weight. Then one can use the equation relating plasma volume and hematocrit to estimate ECW deficit by substituting  $(0.2 \times \text{body wt.})$  for  $(0.045 \times \text{body wt.})$ .

$x$  liters ECW deficit =

$$\frac{(PCV_2 - PCV_1)}{PCV_2(1 - PCV_1)} (0.2 \times \text{body wt.})$$

## Equation III.

Derivation of the equation for approximating the  $\text{Na}^+$  deficit in patients with hyponatremia:

The derivation is based on the fact that the osmotic effect of administered  $\text{Na}^+$  is distributed throughout TBW, so that water will move into the ECW compartment as  $\text{Na}^+$  is added until ICW osmolality equals ECW osmolality.

Before  $\text{Na}^+$  Administration

ECW	ICW
Vol. = X	Vol. = y
$[\text{Na}_1^+]$ = a	$[\text{C}_1^+]* = a$

\* $[\text{C}_1^+]$  = concentration of osmotically active solute confined to ICW and equal to  $[\text{Na}^+]$  in the ECW. This in fact is the concentration of  $\text{K}^+$  in the ICW.

After  $\text{Na}^+$  Administration

ECW	ICW
Vol. = $x + n^*$	
$[\text{Na}_2^+]$ = b	Vol. = $y - n^*$ $[\text{C}_2^+] = b$

\*n = volume of  $\text{H}_2\text{O}$  migrating to ECW after adding  $\text{Na}^+$  to ECW.

- (1) Total  $\text{Na}^+$  in the ECW before  $\text{Na}^+$  administration =  $(a)(x)$
- (2) Total  $\text{Na}^+$  in the ECW after  $\text{Na}^+$  administration =  $(b)(x + n)$
- (3) Total  $\text{C}^+$  in the ICW is constant before and after  $\text{Na}^+$  administration.

Therefore,  $(a)(y) = b(y - n)$

$$n = \frac{y(b-a)}{b}$$

- (4) Let  $z = \text{mEq. Na}^+$  administered to change  $[\text{Na}_1^+]$  to  $[\text{Na}_2^+]$ . It must equal the difference between the total ECW  $\text{Na}^+$  before and after  $\text{Na}^+$  administration.

Therefore,  $z = b(x + n) - (a)(x)$

Substitute  $\frac{y(b-a)}{b}$  for n and solve for z.

$$z = (x + y)(b - a)$$

Since, by definition,  $(x + y) = \text{TBW}$ ,  
and  $(b - a) = \text{Na}_2^+ - \text{Na}_1^+$

$$\text{Therefore, } z = (\text{Na}_2^+ - \text{Na}_1^+)(\text{TBW})$$

$$\text{or } z = (140 - \text{Na}_1^+)(0.6 \times \text{body wt.})$$

## Equation IV.

Derivation of the equation for approximating the water deficit in patients with hypernatremia due to water depletion:

## Before Water Administration

ECW	ICW
$[\text{Na}_1^+] = a$	$[\text{C}_1^+]* = a$
$\text{TBW} - X$	

\* $[\text{C}_1^+]$  = concentration of osmotically active solute confined to ICW and equal to  $[\text{Na}^+]$  in the ECW, i.e., the ICW  $\text{K}^+$  concentration.

## After Water Administration

ECW	ICW
$[Na^+] = b$	$[C^+]* = b$
TBW	

\* $[C^+]$  = concentration of osmotically active solute confined to ICW and equal to  $[Na^+]$  in the ECW i.e. the ICW  $K^+$  concentration

- (1) The total body cation content ( $Na^+ + C^+$ ) is unchanged by water administration but its concentration is reduced equally in ECW and ICW

Therefore  $(a)/(TBW-x) = (b)/(TBW)$

$$x = \frac{(a-b)}{(a)} (TBW)$$

- (2) When  $a = Na_{s1}^+$  (or  $Na_s^+$  before  $H_2O$  administration)  $b = Na_{s2}^+$  (or normal  $Na_s^+$  of 140 mEq/L) and  $TBW = (0.6)(body\ wt\ in\ Kg)$  then

x liters of  $H_2O$  deficit =

$$\frac{Na_{s1}^+ - 140}{Na_{s1}^+} (0.6 \times body\ wt)$$

. . .

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# 3...

## Diets

Sheldon Margen & Florence E. Olson

The diet must supply the following essential components (1) Calories for energy (supplied mainly by carbohydrate), (2) protein for growth, tissue repair, and energy, (3) carbohydrate for energy and for prevention of ketosis, (4) fat for essential fatty acids and energy, (5) minerals and vitamins for maintenance of optimal tissue function and electrolyte equilibrium, and (6) water for absorption and transport of foods and waste products, and for excretion. These requirements can be normally met by including the basic foodstuffs as outlined below. (The dietary components are altered as indicated for the needs of the individual.) Personal eating habits, racial and religious restrictions, expense, and availability of foods must be considered in the preparation of any diet.

### Basic Foods for a Well Balanced Diet.

A. Milk\*. Whole or skimmed. Adults, 2 cups (16 oz.). Children, 4 cups (32 oz.).

B. Vegetables Two or more servings.

1. Starchy (e.g., potatoes) or additional cereal foods,  $\frac{1}{2}$  cup (100 Gm.).

2. Cooked, preferably yellow,  $\frac{1}{2}$  cup (100 Gm.).

3. Raw (salad or juice),  $\frac{1}{2}$ -1 cup (100-200 Gm.).

C. Fruits. Two or more servings.

1. Raw (citrus or tomato often),  $\frac{1}{2}$  cup (100 Gm.).

2. Other (preferably colored and not sweetened),  $\frac{1}{2}$  cup (100 Gm.).

D. Eggs\*. Three to 5 per week.

E. Meats, cheese, fish, legumes\*. One or more servings of one of the following:

1. Low-fat meats, one serving (3-4 oz.).

2. Regular meats, one serving (3-4 oz.).

3. Cheddar or American cheese, 1 oz.

4. Cottage cheese,  $\frac{1}{2}$  cup.

5. Cooked beans (mature),  $\frac{1}{2}$  cup (100 Gm.).

F. Cereal or bread Whole grain or enriched cereal or bread, 2 or more portions [one portion =  $\frac{1}{2}$  cup or 100 Gm. cooked cereal or 1-2 slices of bread (25 Gm./slice)].

G. Fats and oils. Butter or other fat, 2 or more Tbsp. daily. For increased essential fatty acids (EFA, polyunsaturated), include one of the following in the diet

1. Cottonseed oil, corn oil, soybean oil, safflower oil.

2. Nuts (walnuts preferred).

3. Special margarine (high EFA content).

When preparing the food, always make the servings attractive to sight, taste, and smell, and serve at the proper temperature. The best planned diet is useless unless it is eaten by the patient.

### Modifying the Basic Diet.

A. Increased. All or part of the diet must be increased to compensate either for increased activity or increased metabolism, as in thyrotoxicosis, tissue injury, and fever

B. Decreased In obesity, the diet should have fewer calories from carbohydrates and fat.

C. Restricted Some diseases require specific restrictions or variations of one or more of the basic dietary constituents

D. The texture of foods and the frequency of feedings may need to be changed, as in gastrointestinal disorders.

E. The importance of well planned meal patterns so that the basic (essential) foods will be included must be emphasized to all patients. Poor eating habits may be contributing factors in many illnesses. Patients placed on corrective diets must not be permitted to resume improper eating habits that caused the original problem, i.e., the obese patient.

\*High-protein foods.

## PRINCIPAL TYPES OF DIETS

The following diets are planned around the basic foods (listed above) which form the nucleus of a well-balanced diet. Reference is made in the diets to carbohydrate content of foods, protein concentration and types of protein and fat (including polyunsaturated fats). These foodstuffs are analyzed in the charts which follow.

### Sippy Diets

Progressive nonirritating acid-buffering diets taken on a regular schedule

#### Composition

Stage I 3 oz (90 ml) half milk and half cream every hour from 7:00 a.m. to 7:00 p.m.

Stage II Stage I plus 3 feedings of refined cereal (3 oz /serving) and one soft cooked egg t i d

Stage III Stage II plus creamed soups and pureed vegetables

Stage IV 3 oz (90 ml) milk and cream every hour plus regular small feedings of lean meat, potato, pureed vegetables, refined cereals and breads, custard, puddings, cream and butter.

**Restrictions:** Meat extracts, bran, raw vegetables and fruits, tea, coffee, condiments, spices, alcohol and carbonated beverages.

If the high-caloric components and butter fat content of the above diet are contraindicated, use nonfat milk powder 1/2 cup to one cup of water in place of milk and cream for 3 oz feeding, or combine this mixture with an equal quantity of homogenized milk. In stage III and IV use boiled, baked or broiled chicken and fish in place of egg (reduce to one per day).

### Modified Meulengraecht's (Bland) Diet.

Use 5-6 feedings of smooth nonirritating food. (See instructions under bland diet.)

7 a.m. Bland fruit juice or strained fruit. Cooked refined cereal, milk, toasted white bread, butter, jelly, tea.

10 a.m. Custard or plain gelatin dessert with cream.

12 noon Tender meat, Broiled beef patty, ground lean meat, baked broiled or boiled chicken or fish. Refined starchy foods as baked potato (no skin), steamed rice. Smooth cooked or strained fruit. Plain crisp cookie (arrowroot). Tea, Melba toast, butter or margarine.

3 p.m. Tapioca or rice pudding, milk (hot or cold).

5 p.m. Bland, strained cream soup. Tender meat (see 12:00 noon) or egg, cottage

cheese. Vegetable purée. Toasted white bread or soda crackers, butter, jelly. Plain ice cream or smooth cooked fruit tea.

8 p.m. Hot milk, Melba toast or cooked refined cereal with milk. Crisp, toasted white bread, rusk, or zwieback with butter.

### Bland Diet

A normal diet modified to be smooth, nonirritating, and bland in taste. May also be used as low-residue diet (use pureed cooked vegetables and fruits).

**Composition:** Lean meats, fish, poultry, eggs, cottage cheese, milk, buttermilk, potato, pureed or whole cooked vegetables and fruits, diluted orange juice, ripe banana, refined cereals and breads, custard, pudding, plain ice cream, gelatin desserts, cream, butter, margarine, salad oil, salt, sugar, coffee and tea in moderation.

Meals should not be large, small interval feedings are preferred. Always give one feeding at bedtime.

**Restrictions:** Fried foods, raw vegetables and fruits (note exceptions), all gas-forming vegetables or those with strong juices, fruits with seeds and skins, bran, whole grain cereals or breads, highly seasoned foods, carbonated beverages, and alcohol.

### Diabetic Diet (See chart on p. 82)

**Composition:** A balanced measured diet divided into 3 meals and 3 snacks.

**Restrictions:** Sugars or excessive amounts of starches and other high-carbohydrate foods.

### Low-fat, Nongas-forming Diet

**Composition:** Lean meat, fish, poultry, skimmed milk or buttermilk, cottage cheese, cereal products, bread, vegetables and fruits except those listed below, gelatin desserts, sherbet, puddings without cream, sugars and jellies.

**Restrictions:** Pork, ham, bacon, sausage and cold cuts, all fat meat, gravies, all cheese except cottage cheese, cream, butter, margarine, mayonnaise, oil, nuts, chocolate, pastries, and any fried food. Restrict also gas-forming foods such as the cabbage family, onions, turnips, cucumbers, radishes, green peppers, dried peas, beans and other legumes, melons, raw apples, and all highly seasoned foods.

### High-protein, High-carbohydrate, Low-fat Diet.

**Composition:** A low-fat diet with meats placed on large servings of lean meat, fish and fowl, skimmed milk (may use nonfat milk

powder,  $\frac{1}{2}$  cup to one cup water) or buttermilk, cottage cheese, cereal, breads, fruit juices, sugar, and jelly. Add nonfat milk powder to other foods (e.g., ground meats, cereal, fat-free soups). The physician should specify the amount of protein desired in the diet.

**Restrictions:** Same as for low-fat, non-gas-forming diet.

#### High-residue Diet.

**Composition:** A normal diet with a maximum of bulk. All of the basic foods with extra servings of whole grain cereals and breads, vegetables, fruits, and an adequate amount of fluids.

**Restrictions:** None.

#### Cholesterol Lowering Diet. (See chart on p. 51.)

**Composition:** A diet high in polyunsaturated fatty acids, which are of vegetable origin. Meat must be trimmed of fat.

**Restrictions:** Limited use of eggs, meat and butter.

#### High-calorie, High-protein, High-vitamin Diet.

A normal diet containing extra foods high in protein and all of the vitamins.

**Composition:** All of the basic foods with increased amounts of meat, fish, poultry, liver, eggs, milk, cheese, whole grain cereals, carrots, green vegetables, citrus fruits, butter or margarine.

**Restrictions:** None.

#### Low-calorie Diets. (See chart on p. 50.)

Bulky diets containing adequate protein which are lower in calories than the patient's daily requirement.

Help the patient to reevaluate his present eating habits, e.g., omission of breakfast or inadequate breakfast leads to "snacking" of high-calorie food lacking in good nutrients. (A very large meal at night tends to decrease the appetite for breakfast.) The desire for high-calorie foods can be controlled by giving the proper amounts of basic foods in a well regulated daily pattern of food intake.

#### Low-protein Diet.

A normal diet with the protein foods limited to the minimum but adequate amount. The physician should specify protein intake in Gm. protein per day.

#### Special Elimination Diets.

A normal diet containing no foods suspected of causing allergic reactions. Such reactions are produced most frequently by wheat, eggs, and milk, less frequently by citrus fruits, nuts, chocolate, and fish. Other foods may infrequently cause reactions.

More specialized diets have been prepared by allergists and are used both diagnostically and therapeutically. Consult books on allergy for these diets.

#### Low-purine Diet.

Diet low in nucleoproteins.

**Restrictions:** The following are strictly forbidden: Liver, kidney, sweetbreads, sardines, anchovies, brains, whole grain products, gravy, soups, meat extractives, asparagus beans, cauliflower, peas, lentils, and mushrooms.

Limited quantities of other meats, fish, and fowl may be allowed.

**Composition:** All other foods are allowed. Most protein to be derived from eggs and dairy products.

#### Low-sodium Diet. (See chart on p. 51.)

The degree of sodium restriction is variable. In general, the lower the sodium content, the less palatable the diet, therefore, patients will usually not adhere faithfully to diets very low in sodium (200-500 mg./day).

Foods must be prepared without salt or any of the herb-flavored or smoke-flavored salts. Omit all cured meats, canned foods with added salt, pickles, sauces, salad dressings, bouillon cubes, salted nuts, potato chips, crackers, baking powder or baking soda. Most "prepared" food has some salt added (read label). Avoid the high-sodium foods listed on p. 49. The essential foods on this list can be served in limited quantities only. The following add flavor in the absence of salt: all dry or fresh herbs, lemon, vinegar, and tomatoes.

### CARBOHYDRATE CONTENT OF FOODS

#### Rough Approximation.

The following approximate values are sufficient in most cases for calculating the carbohydrate content of foods. An "average serving" is about  $\frac{1}{2}$  cup cooked or one cup of raw vegetables or fruits.

Average Serving	Amount of CHO	Total Calories
Vegetable	4-8 Gm.	25
Fruit	12-15 Gm.	50
Slice bread, potatoes, corn, beans, cereals	15-20 Gm.	75

## 48 Sodium Content of Foods

### Close Approximation

When more precise calculations are necessary determine the carbohydrate content of foods from the following lists

**3% Vegetables** One portion of  $\frac{1}{2}$  cup (100 Gm ) contains 2 Gm protein 3 Gm carbohydrate and 20 Calories

Asparagus	Sauerkraut
Broccoli	Stringbeans young
Brussels sprouts	Summer squash
Cabbage	Tomatoes
Cauliflower	Watercress
Celery	Greens
Cucumber	Beet greens
Eggplant	Chard
Lettuce (all types)	Collards
Mushrooms	Dandelion
Okra	kale
Parsley	Mustard
Pepper green	Poke
Radishes	Spinach
Rhubarb	Turnip greens

**7% Vegetables** One portion of  $\frac{1}{2}$  cup (100 Gm ) contains 2 Gm protein 7 Gm carbohydrate and 38 Calories

Beets	Green peas	Rutabagas
Carrots	Onions	Turnips
Globe artichoke	Pumpkin	Winter squash

**20% Vegetables & Cereal Food** One portion of  $\frac{1}{2}$  cup (100 Gm ) contains 2 Gm protein 20 Gm carbohydrate and 88 Calories

Cooked beans	Corn
Cooked grits	Parsnips
Cooked macaroni	Potato (white)
Cooked noodles	Water chestnut
Cooked rice	Sweet potato or yam ( $\frac{1}{4}$ cup)
Cooked spaghetti	

**10 15% Fruits** One portion of  $\frac{1}{2}$  cup (100 Gm ) contains 10 Gm carbohydrate and 40 Calories Most fresh unsweetened cooked or frozen fruits (except those listed in 20% fruit list)

Apples	Melons (all types)
Apricots	Oranges
Berries (all types)	Peaches
Grapefruit	Pears
Lemons	Pineapple
Limes	Tangerines

**20% Fruits** One portion of  $\frac{1}{2}$  cup (100 Gm ) contains 20 Gm carbohydrate and

80 Calories Includes sweetened canned fruit and the following fresh or dried fruits

Banana	Dried fruits $\frac{1}{4}$ cup
Figs (fresh)	(prunes apricots
Grapes	peaches dates not
Plums	cooked)

**Starch List** The following portions contain 2 Gm protein 15 Gm carbohydrate and 68 Calories

- 1 slice (25 Gm ) bread (any kind but pastry type breads)
- $\frac{1}{2}$  cup (100 Gm ) cooked cereal
- $\frac{3}{4}$  cup (15 20 Gm ) dry (puffed or flake) cereal
- 1 small muffin or roll (2 inches in diameter)
- 2 graham crackers
- 3 saltines (2 inches square)
- 3 Ry Kriap (2 x 3 inches)

## CALORIE CONTENT OF BEVERAGES

The following common beverages contain the stated number of Calories/oz

- Black coffee (1)
- Tea (0)
- Ginger ale (12)
- Beer (12)
- Other carbonated beverages (15)
- Dry wine (25)
- Sweet wine (40)
- Liquors (75)

The caloric content of beer wine and liquors are derived mainly from alcohol

## SODIUM CONTENT OF FOODS (Without Added Salt)

### Foods Very Low in Sodium (Trace Amounts)

Coffee	Oil
Granulated sugar	Plain matzoth
Granulated gelatin	Sweet butter
Jellies	Tea
Natural herbs	

### Fresh Foods Containing Less Than 5 mg. Sodium/100 Gm. Portion.

Asparagus	Nuts, unsalted	Potatoes
Corn*	(2 mg./100 Gm.)	Pumpkin
Cucumbers	Gm.)	Squash (all types)
Dried beans	Okra	Tomatoes
Eggplant	Peas*	Waxed beans
Green beans	Parasnips	Yellow turnips
Lima beans*	Peppers	
Most fruits		

Cereals contain about 4-6 mg./100 Gm. dry weight. The following, when cooked or prepared without added salt, deliver about 1 mg. sodium/serving. (Note: Read label, Some "quick-cooking" enriched cereals contain a sodium compound.) Oatmeal, rolled wheat, Ralston, Wheatena, Wheathearts, cracked wheat, farina, cornmeal, grits, rice, Puffed Rice, Puffed Wheat, Shredded Wheat, and Sugar Pops.

### Foods Containing 5-25 mg. Sodium/100 Gm. Portion (or as Specified),

Broccoli	Dried peas
Bread, unsalted	Dry curd cottage cheese
(7 mg./25 Gm. slice)	
Brussels sprouts	Onions
Cabbage	Parasnips
Cauliflower	Radishes
Cucumbers	Sweet potatoes

### Foods High in Sodium Content (Values/100 Gm. Portion or as Specified),

Artichoke (40 mg.)	Shellfish (75-400 mg.)
Beets (40 mg.)	Meats (unsalted):
Beet greens (130 mg.)	Fish (including
Bread, commercial (180 mg./25 Gm. slice)	marine-type but not shellfish),
Carrots (50 mg.)	beef, pork,
Celery (100 mg.)	veal, chicken,
Chard (100 mg.)	turkey (70-90 mg.)
Egg, 1 medium (70 mg.)	White turnips
Kale (80 mg.)	(40 mg.)
Sausages (very high in sodium)	

### Sodium Content of Beverages.

Beer (20 mg./8 oz.)	Ginger Ale (20 mg./8 oz.)
Coca-Cola (5 mg./8 oz.)	Low-sodium milk (5 mg./100 ml.)
Coffee, tea (virtually no sodium)	Milk, whole or skimmed (50 mg./100 ml.)
Buttermilk (130 mg./100 ml.)	

\*Frozen lima beans, corn, and peas contain much more sodium than when served fresh.

### POTASSIUM CONTENT OF FOODS

All foods in the natural state are rich sources of potassium.

All raw or cooked fruits, with the juices eaten, are good sources of potassium. The following are excellent sources (300 mg. or more per 100 Gm. portion): apricots, bananas, nectarines, all dried fruits.

Nearly all vegetables contain 300 mg. of potassium per 100 Gm. portion, but proper cooking or use of vegetable juices is necessary if the potassium is to be retained. Potatoes, dried peas, and beans are especially high in potassium.

All meats, chicken, and fish (but not shellfish) supply about 300 mg. of potassium per 100 Gm. portion.

Milk contains 150 mg./100 ml., or over 300 mg./cup.

Nuts contain about 600 mg./100 Gm. (One cup of nuts is 100-150 Gm.)

Miscellaneous foods high in potassium are tea, coffee, cocoa, chocolate, molasses, bran, wheat germ, and brewer's yeast (dried yeast)

### TUBE FEEDINGS

Tube feedings are employed when patient is unable or unwilling to take food by mouth. A convenient means of administering the feedings is with a small polyethylene tube passed intranasally. Many food mixtures may be given, the only requirements are that the food be fluid or in a suspension of very small particles.

Protein hydrolysates are often irritating. Formulas containing egg tend to occlude the lumens of small tubes. Excellent formulas can be prepared by using milk (occasionally clots in tube), calcium caseinate, Lonalac<sup>®</sup>, strained meats, lactose, sucrose, or glucose. Fats such as salad oil may be added if emulsified with polysorbate 80 (Tween 80<sup>®</sup>) or a similar agent. Vitamins and minerals are added as indicated.

Caution: (1) Begin with more dilute material and administer slowly. (2) The best rate is usually 3 L./24 hours. (3) Never administer over 200 ml. at a time. (4) If foods must be given rapidly, warm to body temperature. (5) If gastric distention is suspected, aspirate with a gastric tube. (6) Use with care in comatose patients to prevent aspiration.

Examples of tube feeding formulas are as follows.

## 50 Tube Feedings

- (1) Low calcium high protein diet Supplies  
3000 Calories/3 L (1 Cal /ml ) contains  
133 Gm protein

Strained canned baby meat 400 Gm (4 cans)  
Tomato juice 1800 ml  
Prune juice 90 ml  
All purpose Soyalac® 200 Gm  
Lactose or sucrose 315 Gm (1 1/3 cups)  
Water q s ad 3000 ml

- (2) Inexpensive high protein formula Supplies  
3000 Calories/3 L (1 Cal /ml ) contains  
120 Gm protein

Homogenized milk 2200 ml  
1/2 milk and 1/2 cream 600 ml  
Eggs 6  
Dextrin Maltose® 7 Tbsp  
lactose or sucrose

- (3) Low sodium high protein formula Sup  
plies 3000 Calories/3 L (1 Cal /ml ) con  
tains 150 Gm protein 78 mg sodium  
Either of the following may be used  
(1) Lonalac® 600 Gm  
Water q s ad 3000 ml

- (2) Low sodium milk 3000 ml

## PROTEIN CONTENT OF FOODS

	Portion	Protein (Gm )	Fats (Gm )	Carbohydrate (Gm )	Approximate Cal /Portion
Low fat meats*	1 oz cooked	7	2		45
Regular meats†	1 oz cooked	7	5		65
High fat meats‡	1 oz cooked	7	5 15		65 145
Cottage cheese	1/4 cup (2 oz )	7	2	2	50
Cooked beans (mature)	1/2 cup (100 Gm )	7		21	110
Nuts (walnuts)	1/3 cup (1 oz )	5	21	5	230
Whole milk	1 cup (8 oz )	9	10	12	165
Skimmed (nonfat) milk or cultured buttermilk	1 cup (8 oz )	9		13	90

\*Poultry fish shellfish liver heart sweetbreads

†All other lean meats and lean cold cuts

‡Pork ham bacon fatty meats sausage meats luncheon meats

## LOW CALORIE DIETS

	600 Cal (50 Gm Protein)	800 Cal (60 Gm Protein)	1000 Cal (63 Gm Protein)	1200 Cal (72 Gm Protein)	1400 Cal (80 Gm Protein)	1600 Cal (100 Gm Protein)
Liquid skimmed milk*	2 cups	2 cups	2 cups	2 cups	2 cups	3 cups
Low calorie cottage cheese	1/2 cup	3/4 cup†	3/4 cup†	3/4 cup†	3/4 cup†	
Low fat meats	2 oz	3 oz †	3 oz †	3 oz †	3 oz †	4 oz
Regular meats		2 oz	2 oz	3 oz	4 oz	4 oz
Oil (cotton corn saflower)		2 tsp	3 tsp	4 tsp	4 tsp	5 tsp
Walnuts			6 nuts	6 nuts	6 nuts	8 nuts
Butter or mar garine					1 tsp	2 tsp
Cereal bread	1/2 cup and 1 slice	1/2 cup and 1 slice	1/2 cup and 1 slice	1/2 cup and 1 slice	1/2 cup and 1 slice	1/2 cup and 1 slice
20% vegetable				1/2 cup	1/2 cup	1/2 cup
7% vegetable	1/2 cup	1/2 cup	1/2 cup	1/2 cup	1/2 cup	1/2 cup
3% vegetable	As desired	As desired	As desired	As desired	As desired	As desired
10% fruit	1 cup	1 cup	1 1/2 cups	1 1/2 cups	1 1/2 cups	2 cups

\*For 2 cups skimmed milk may substitute 2 oz low fat meats

†For 800 1400 Calorie diets give either 3/4 cup cottage cheese or 3 oz low fat meats

## SODIUM-RESTRICTED DIETS

	Approx. 500 mg Sodium			Approx. 1000 mg Sodium		
	1400 Cal	2200 Cal	Na (mg.)	1400 Cal.	2200 Cal	Na (mg.)
Salt-free* low-fat meats	4 oz	4 oz	96	4 oz	4 oz	96
"Salt-free" regular meats	4 oz	4 oz	96	4 oz	4 oz	96
Eggs	One	One	70	One	One	70
Regular milk*						
Skimmed	1 cup	---	120	2 cups	---	240
Whole	---	1 cup		---	2 cups	
Butter	2 tsp (salt-free)	4 tsp (salt-free)	--	2 tsp † (regular)	2 tsp (regular)	98
Oil or salt-free dressing	1 Tbsp	2 Tbsp	---	1 Tbsp	2 Tbsp	---
Bread or Cereal	2 portions of either (salt-free)	3 portions of either (salt-free)	(10) or (15)	2 portions † (regular)	2 portions (regular)	360
				---	1 portion (salt-free)	5
Vegetables (unsalted)						
20%	1 portion	1 portion	5	1 portion	1 portion	5
7% ‡	1 portion	1 portion	7	1 portion	1 portion	7
3% ‡	As desired	As desired	10	As desired	As desired	10
Fruits						
10%	2 cups	2 cups	16	2 cups	2 cups	16
20%	---	1 cup	8	---	1 cup	8
Nuts (unsalted)	---	1/3 cup	---	---	1/3 cup	---
Jam or jelly	1 Tbsp	2 Tbsp	--	1 Tbsp	2 Tbsp	---
TOTALS Protein	61 Gm	86 Gm		90 Gm	97 Gm	
Fat	59 Gm	115 Gm		49 Gm	105 Gm	
GHO	130 Gm	204 Gm		142 Gm	216 Gm	
Sodium	434 mg	443 mg		998 mg	1011 mg	

\*To reduce sodium content 100 mg., use low-sodium milk

†Use regular bread and butter to increase sodium and keep constant

‡Restrict high-sodium vegetables (over 25 mg / 100 Gm.) to 3 servings weekly.

 CHOLESTEROL-LOWERING DIET,  
 HIGH EFA (POLYUNSATURATED) DIET

	1600 Calories (80 Gm. Protein)	2000 Calories (100 Gm. Protein)	2500 Calories (120 Gm. Protein)
Skimmed milk	3 cups (720 ml.)	4 cups (960 ml.)	2 cups (480 ml.)
Whole milk	-	-	2 cups (480 ml.)
Low-fat meat (twice a day)*	3 oz. (90 Gm.)	3 oz. (90 Gm.)	4 oz. (120 Gm.)
Regular meat (once a day) †	3 oz. (90 Gm.)	3 oz. (90 Gm.)	4 oz. (120 Gm.)
Egg (or eliminate and substi-	-	1 (50 Gm.)	1 (50 Gm.)
Bacon (or substitute nuts or low-fat meat)	-	-	2 strips (10 Gm.)
High EFA margarine	2 tsp. (10 Gm.)	2 tsp. (10 Gm.)	2 tsp. (10 Gm.)
Oil (50% linoleic acid) or salad dressing	2 Tbsp. (30 Gm.)	3 Tbsp. (45 Gm.)	3 Tbsp. (45 Gm.)
Nuts (walnuts)	1/4 cup (25 Gm.)	1/3 cup (45 Gm.)	1/2 cup (50 Gm.)
Starch list ‡	2 portions	2 portions	3 portions
3% vegetables§	As desired	As desired	As desired
7% vegetables§	1/2 cup (100 Gm.)	1/2 cup (100 Gm.)	1/2 cup (100 Gm.)
20% vegetables§	1/2 cup (100 Gm.)	1/2 cup (100 Gm.)	1/2 cup (100 Gm.)
10% fruit ‡	4 portions	5 portions	5 portions

\*Fowl, fish, shellfish, liver, breast, sweetbreads. May substitute regular meat once a day.

†All other lean meats and lean cold cuts. May substitute low-fat meat twice a day.

‡See p. 48

§See p. 48

## DIABETIC DIET

(A calculated diet with regulated amounts of protein, fat, and carbohydrate)

Suggested Meal Pattern		1600 Cal.	2000 Cal.	2500 Cal
7 00-8 00 a.m.	10% fruit	1 portion	1 portion	1 portion
	Starch list	1 portion	1 portion	1 portion
	Egg	-	1	1
	Bacon	-	-	2 strips
	EFA margarine, oil	1 tsp. of either	1 tsp. of both	1 tsp. of both
	Skimmed milk	1/2 cup	1/2 cup	-
	Whole milk	-	-	1/2 cup
	Tea or coffee	As desired	As desired	As desired
10 00 a.m.		1/2 cup skimmed milk	1 cup skimmed milk	1/2 cup skimmed milk 1/2 cup 10% fruit
Noon-1 00 p.m.	Clear broth (no fat)	As desired	As desired	As desired
	Low-fat meat	3 oz. (90 Gm.)	3 oz. (90 Gm.)	4 oz. (120 Gm.)
	Starch list	1 portion	1 portion	2 portions
	3% vegetable	As desired	As desired	As desired
	EFA margarine	1 tsp.	1 tsp.	1 tsp.
	Oil or salad dressing	1 Tbsp.	1 Tbsp.	1 Tbsp.
	10% fruit	1 portion	1 portion	1 portion
	Milk	-	1/2 cup skimmed milk	1 cup whole milk
	Tea or coffee	As desired	As desired	As desired
3 00-4 00 p.m.		Portion of 1/4 cup nuts (see bedtime)	Portion of 1/3 cup nuts (see bedtime)	1/4 cup nuts
		1 cup skimmed milk	1 cup skimmed milk	1 cup skimmed milk
6 00-7 00 p.m.	Regular meat	3 oz. (90 Gm.)	3 oz. (90 Gm.)	4 oz. (120 Gm.)
	Vegetables - 20%	1 portion	1 portion	1 portion
	- 7%	1 portion	1 portion	1 portion
	- 3%	As desired	As desired	As desired
	EFA margarine	1 tsp. if not used in a.m.	1 tsp. if not used in a.m.	1 tsp. if not used in a.m.
	Oil or salad dressing	2 or 3 tsp.*	1 1/2 Tbsp.	1 1/2 Tbsp.
	10% fruit	1 portion	1 portion	1 portion
	Tea or coffee	As desired	As desired	As desired
8 00-10 00 p.m. (bedtime)		Finish nuts 1 cup skimmed milk One portion 10% fruit	Finish nuts 1 cup skimmed milk. One portion 10% fruit	1/2 cup skimmed milk, and 1/2 cup whole milk 1/4 cup nuts One portion 10% fruit

\*May have 3 tsp. if none has been used at breakfast



# Skin & Appendages

Rees B Rees, Jr

## Diagnosis of Skin Disorders.

Take a thorough case history from every patient with a skin disease. Do not neglect the role of constitutional factors in production or aggravation of skin diseases (e.g., internal disease, emotional factors, dietary aberrations). Examine the entire body surface in good (preferably natural) light.

## Planning the Treatment.

A bewildering variety of topical agents are available for the treatment of dermatologic disorders. In general, it is better to be thoroughly familiar with a few drugs and treatment methods than to attempt to use a great many.

In planning the treatment it is necessary to consider the individual character of the patient's skin. Dry skins usually require lubricating or softening agents, moist or oily skins usually require greaseless drying agents.

Begin treatment with mild, simple remedies. In general, acute, inflamed lesions are best treated with soothing, nonirritating agents. Chronic, thickened lesions with stimulating or keratolytic agents. Apply a small amount of medication to a small area and observe for 15-20 minutes for skin sensitivity.

Do not change remedies before the agent has had time to demonstrate its effectiveness. However, discontinue the drug immediately if an untoward local reaction develops.

Instruct the patient carefully on how to apply medicaments.

When in doubt about the proper method of treatment, undertreat rather than overtreat.

## General Rules Governing Choice of Topical Treatment of Various Stages of Dermatoses

Note: The choice of treatment will vary with the individual case depending upon the characteristics of the dermatosis, the extent of the lesions, the general character of the patient's skin, previous medication and drug allergies, and other factors.

**A. Acute Lesions** (Recent onset, red, burning, swollen, itching, blistering, or

oozing.) Use wet preparations, such as soaks for lesions localized to extremities (see p. 93), wet dressings for localized lesions of the head, neck, trunk, or extremities (see p. 93), or baths for generalized lesions (see p. 54).

**B. Subacute Lesions** (Intermediate duration, subsiding lesions, and lesions which are less angry in appearance.) Use wet preparations as outlined above, shake lotions (see p. 94), or both.

**C. Chronic Lesions** (Longer duration, quiescent, thickened, encrusted, fissured, scaly.) Use wet preparations or shake lotions (or both) as outlined above, or any of the following emulsions (see p. 94), hydrophilic ointments (see p. 95), pastes (high powder content) (see p. 95), creams such as cold creams and vanishing creams (see p. 95), or greasy ointments (see p. 96).

## Prevention of Complications.

The most common complications of skin diseases are pyoderma, local or systemic spread of infection, overtreatment dermatitis, drug sensitivity reactions, and cosmetic disfigurement.

**A. Pyoderma** Infected, inflamed, or denuded areas of skin are receptive environments for pyogenic organisms introduced by scratching, rubbing, or squeezing of skin lesions. Patients should be instructed to wash their hands frequently and to avoid manipulation of infected areas. Medications should be kept in closed containers and applied with sterile applicators, which should be discarded after use. Crusts and scabs should not be removed except by the physician. If an infection occurs in a hairy portion of the body, special care should be taken in cleansing and shaving the area.

**B. Local or Systemic Spread of Infection** Almost any skin infection may spread by extension or through blood vascular or lymphatic channels. In most cases this complication is

a much greater threat to the patient's health and life than the primary skin infection. A most striking and serious example is the extension of staphylococcal infections of the face to the cavernous sinuses. Lymphangitis, lymphadenitis, septicemia, renal carbuncle, bladder infections and glomerulonephritis may occur as sequelae to primary skin infection. For these reasons it is important to institute vigorous local and systemic measures for the control of skin infections. Systemic antibiotics are ordinarily reserved for serious skin infections or infections associated with systemic reactions, and should be selected on the basis of bacteriologic studies.

**C Overtreatment Dermatitis** This may be avoided if the physician and the patient are aware that undertreatment is preferable to overtreatment and if the patient is warned to avoid overenthusiastic application of topical remedies (either too much or too long).

**D Exfoliative Dermatitis** This complication cannot always be anticipated or avoided but it may be minimized if a careful history of drug sensitivity is obtained before institution of drug therapy. In allergic individuals it is imperative to apply a small amount of topical medication in order to determine hypersensitivity. Drugs which may be required for systemic use (e.g. sulfonamides, antibiotics, or antihistamines) should preferably not be used in topical preparations.

**E Cosmetic Disfiguration** Disfiguration due to skin disorders may be avoided by early, careful treatment of skin lesions and by appropriate dermatologic operative techniques. Self-manipulation of skin lesions, especially on the face and exposed skin areas, should be avoided.

Pillsbury, D M, & others. *Dermatology*. Saunders, 1956.

Sulzberger, M B, Wolf, J, & V H Witten. *Dermatology: Diagnosis and Treatment*, 2nd ed. Year Book, 1961.

## PRURITUS (itching)

"Pruritus is that disagreeable sensation which excites the desire to scratch" (Haffner-reffer). It is the commonest presenting symptom in dermatology, and includes localized or generalized itching, stinging, crawl-

ing and burning sensations. Pruritus is far less well tolerated than pain.

Transient, mild pruritus may be physiologic. Pruritus may be a symptom of specific dermatologic disorders, may be idiopathic or may foreshadow or accompany serious disease of internal origin (lymphomas and other neoplasms, hepatic or biliary disease, diabetes mellitus, nephritis, or drug intoxication or habituation). Perhaps the most common cause of generalized pruritus is excessive dryness of the skin, as in borderline forms of ichthyosis, senile degeneration complicated by irritation with soaps, and low humidity due to artificial heating and cold weather. Other causes are pressure and chafing, chemical irritants (including drugs), food and other allergies, and emotional factors.

## Treatment

**A General Measures** Foods should be simple, avoid rich and spicy foods. Test diets or elimination diets are indicated for suspected food allergies (see p 47). If pruritus is believed to be primarily a manifestation of an emotional disorder, direct therapy accordingly. External irritants (e.g., rough clothing, occupational contactants) should be avoided. Soaps and detergents should not be used by persons with dry or irritated skin. Starch baths may be used (see above). Nails should be kept trimmed and clean. Avoid scratching, if possible. Unnecessary medications should be discontinued since medication itself often produces pruritus.

**B Specific Measures** Remove or treat specific causes whenever possible.

## C Local Measures

1 Shake lotions, emulsions, and ointments, incorporating the volatile analgesics and antipruritics listed in the table on p 94, may be of value in relieving itching.

2 If the skin is too dry, softening agents may afford relief, e.g., rose water ointment (R 30, p 95). An excellent principle for dry skin is to wet it, as in a bath (to hydrate the keratin) and then apply petrolatum to the wet skin to trap the moisture.

3 If the skin is too moist, drying agents may afford relief, e.g., wet dressings, soaks (R 1-7, p 93), shake lotions (R 13-15, p 94), and powders (R 9-11, p 93) (especially if the process is acute).

4 Tub baths - Generalized pruritus may often be effectively controlled by lukewarm baths, 15 minutes 2-3 times daily. After bathing the skin should be blotted (not rubbed) dry. (Caution: Avoid excessive drying of skin by overbathing, prolonged bathing periods, and exposure to drafts after bathing.) Useful bath

formulations are as follows (1) Starch and soda bath 1-3 cups of starch and one cup of sodium bicarbonate dissolved thoroughly in one tubful (50 gallons) of lukewarm water (Soda may be omitted) (2) Tar bath Dissolve 50-100 ml Coal Tar Solution, U.S.P., in one tubful (50 gallons) of warm water (Watch for sensitivity)

#### D Systemic Antipruritic Drugs

1 Calcium gluconate injection, 10%, 10 ml I V slowly, once daily or every other day p r n

2 Antihistaminic and antiserotonin drugs may be tried in certain cases of pruritus of allergic or undetermined etiology

3 Epinephrine injection, 0.25-1 ml of 1:1000 solution every 4 hours may be of value in acute cases which may be due to allergy (e.g., urticaria)

4 Phenobarbital, 15-30 mg ( $\frac{1}{4}$ - $\frac{1}{2}$  gr) 2-4 times daily, may provide useful sedation in agitated or distracted patients Barbiturates themselves rarely produce dermatitis

5 Corticotropin or the cortisones (see Chapter 17).

#### Prognosis

Elimination of external factors and irritating agents is often successful in giving complete relief of pruritus Pruritus accompanying specific skin disease will subside when the disease is brought under control Idiopathic pruritus and that accompanying serious internal disease may not respond to any type of therapy

Shelley, W.B., & R.P. Arthur The neurohistology and neurophysiology of the itch sensation in man Arch Dermat 76:296-323, 1955

## COMMON DERMATOSES

### DERMATITIS VENENATA (Contact Dermatitis & Dermatitis Due to Plant Irritants)

#### Essentials of Diagnosis

- Erythema followed by pruritic papules and vesicles in area of contact with suspected excitant
- Weeping, crusting, secondary infection
- History of previous "reaction" to suspected agent
- Patch test with suspected agent is positive

Asymmetric distribution and a history of contact help distinguish dermatitis venenata from other skin lesions Differentiation may be difficult if the area of involvement is consistent with other types of skin disorders, e.g., scabies and dermatophytid and sweat retention reactions on the hands, seborrheic dermatitis on the scalp, and atopic dermatitis and eczema on the body

#### General Considerations

Dermatitis venenata is an acute or chronic dermatitis which results from direct skin contact with chemicals or other irritants (e.g., poison ivy) Lesions are most often on exposed parts Four-fifths of such disturbances are due to excessive exposure to or additive effects of primary or universal irritants (e.g., soaps, detergents, organic solvents) Others are due to actual contact allergy or idiosyncrasy

#### Clinical Findings

A Symptoms and Signs Itching, burning, and stinging are often extremely severe distributed on exposed parts or in bizarre asymmetric patterns The lesions consist of erythematous macules, papules, and vesicles The affected area is often hot and swollen with exudation crusting, and secondary infection The pattern of the eruption may be diagnostic (e.g., typical linear streaked vesicles on the extremities and erythema and swelling of the genitals in poison oak dermatitis) The location will often suggest the cause scalp involvement suggests hair tints, lacquer, shampoos, or tonics, face involvement, creams, soaps, shaving materials, neck involvement, jewelry, fingernail polish, etc

**B Laboratory Findings** The patch test may be useful but has serious limitations. In the event of a positive reaction, a control test must be done on another individual to rule out primary irritation.

#### Prevention

**A. Prevent Re-exposure to Irritants:** Avoid soaps and detergents. Use so-called "nonallergenic cosmetics" or eliminate cosmetics entirely. Protective rubber gloves may be used but are seldom indicated. In such cases an inner cotton glove must be used. Protective (barrier) creams are almost useless. It may be necessary to change occupation or duties if occupational exposure is otherwise unavoidable.

Plant irritants (especially *Rhus* species, e.g., poison ivy) should be destroyed by manual removal or by chemical means (2,4-D or dichlorophenoxyacetic acid) near dwellings and in frequented areas.

**B Prompt and thorough removal of irritants** by prolonged washing or by removal with solvents or other chemical agents may be effective if done very shortly after exposure. In the case of *Rhus* toxin, thorough washing with soap and water must be done within a few minutes if it is to be of any value.

**C Most well-controlled studies indicate** that injection or ingestion of *Rhus* antigen is of no practical clinical value.

#### Treatment.

**A General Measures:** Corticotropin by injection or one of the cortisones by mouth daily may be tried (see Chapter 17).

**B Local Measures:** Treat the stage and type of dermatitis (see p. 53).

1. **Acute weeping dermatitis** - Do not scrub lesions with soap and water. Apply soothing solutions (see p. 93). If the eruption becomes generalized, use the soothing starch and soda antipruritic bath described on p. 54. Shake lotions (§ 13-15, p. 94) may be indicated instead of wet dressings or in intervals between wet dressings, especially for involvement of intertriginous areas or when oozing is not marked. Lesions on the extremities may be bandaged with wet dressings. Hydrocortisone and related preparations in lotion, cream, or ointment applied sparingly 2-4 times daily may be very helpful.

2. **Subacute dermatitis (subsiding)** - Use shake lotions.

3. **Chronic dermatitis (dry and lichenified)** - Treat with hydrophilic, greasy ointments or

creams. Tars are perhaps most useful in this stage of the dermatitis.

#### Prognosis.

*Dermatitis venenata* is self-limited if re-exposure is prevented. Spontaneous desensitization may occur. Increasing sensitivity to industrial irritants may necessitate a change of occupation.

Baer, R. L., & V. H. Witten. Allergic eczematous contact dermatitis. Part I, pp. 7-38, in *Year Book of Dermatology and Syphilology*, Year Book, 1956-57.

Kligman, A. M. Hyposensitization against *Rhus* dermatitis. *Arch. Dermat.* 78:47-70, 1958.

### ERYTHEMA NODOSUM

#### Essentials of Diagnosis

- Sudden appearance of painful red nodules usually on anterior surfaces of both legs.
- Regression in a few weeks to resemble a contusion.
- History or findings of infection or drug sensitivity in some cases.

Syphilitic nodules and gummas are painless, often unilateral, and are not red. In the late stages erythema nodosum must be distinguished from simple contusions and bruises. Erythema multiforme occurs in generalized distribution.

#### General Considerations.

Erythema nodosum is a symptom complex characterized by tender, erythematous nodules which appear most commonly on the extensor surfaces of the legs. It usually lasts about 6 weeks, and may be recurrent. It may be associated with various infections (primary coccidioidomycosis, primary tuberculosis, streptococcosis, rheumatic fever, or syphilis) or may be due to drug sensitivity (notably sulfathiazole).

#### Clinical Findings

**A Symptoms and Signs** The swellings are exquisitely tender, and are usually preceded by fever, malaise, and arthralgia. The nodules are most often located on the anterior surfaces of the legs below the knees but may occur (rarely) on the arms, trunk, and face. The lesions, 1-10 cm in diameter, are at

first pink to red, with regression, all the various hues seen in a contusion can be observed. The nodules occasionally become fluctuant, but they do not suppurate.

**B Laboratory Findings** The histologic finding of fat replacement atrophy in the corium or dermis is strongly suggestive of erythema nodosum. Hilar adenopathy is often seen on chest x-ray.

#### Treatment.

**A General Measures** Eliminate or treat the "specific" cause, e.g., systemic infection and exogenous toxins. Rest in the hospital may be advisable. Focal infections should be treated, although this does not appear to influence the course of the disease. Systemic therapy directed against the lesions themselves may include tetracycline drugs, 250 mg q.i.d. for several days, or corticosteroid therapy (see Chapter 17) unless it is contraindicated (tuberculosis must be ruled out).

**B Local Treatment** is usually not necessary. If the lesions are troublesome treat according to stage and type of dermatitis (see p. 53).

#### Prognosis.

The lesions usually disappear after about 6 weeks, but they may recur. The prognosis depends in part on that of the primary disease.

**Beerman, H.** Erythema nodosum - a survey of some recent literature. *Am J M Sc* 223:433-44, 1952.

## ERYTHEMA MULTIFORME

#### Essentials of Diagnosis

- Symmetric violaceous, polymorphic skin lesions (macules, papules, nodules, bullae) with a history of recurrence.
- Mostly on extensor surfaces, may be on palms, soles, or mucous membranes.
- History or evidence of systemic disease or drug sensitivity.

Differentiation from urticaria, pemphigus, and dermatitis herpetiformis is based largely on clinical and morphologic grounds (recurrent

attacks, multiplicity of types of erythematous mucous membrane and skin lesions). In erythema multiforme there is usually some constitutional reaction, including fever.

#### General Considerations.

Erythema multiforme is an acute inflammatory, polymorphic skin disease of multiple or undetermined origin. It may occur as a primary skin disorder or as a skin manifestation of systemic infection, malignant or chronic disease of the internal organs, or as a reaction to an ingested drug or injected serum. Ropes simplex virus and infestations such as ascariasis have also been implicated. The lesions occur predominantly in the spring and fall, and are most common in young people.

#### Clinical Findings

**A Symptoms and Signs** The onset is sudden, often accompanied by burning sensations. There may be soreness of the oral, ocular and genital mucous membranes. Several lesions may be present with relatively little discomfort. Slight to severe headache, backache, and malaise may occur, and slight to moderate fever.

The principal sign is the symmetric distribution of grouped or isolated crops of violaceous, edematous papules, macules, or nodules, 0.5-1 cm in diameter, with dome-shaped surfaces. The lesions enlarge and become purplish. The term "multiforme" signifies that the lesions may have many sizes and shapes. In addition to those just listed, there may be vesicles, bullae, pustules, urticarial lesions, and hemorrhagic alterations. The bullae may resemble those of pemphigus, but usually are surrounded by an erythematous halo. A rather characteristic lesion is the erythema iris (herpes iris), the "bull's eye" pattern formed by an erythematous papule with central clearing. Lesions are usually on the extensor surfaces but may appear anywhere, such as the palms and soles. Mucous membrane ulcerations (aphthae) are frequent. A rare type, erythema perstans, may be present for months or years.

**B Laboratory Findings** There are no characteristic laboratory findings. Histologic changes may be suggestive but are not pathognomonic.

#### Complications

Erythema multiforme may be complicated by visceral lesions (e.g., pneumonitis, myocarditis, nephritis).

**Prevention**

Avoid all unnecessary medications in patients with a history of erythema multiforme

**Treatment.**

**A General Measures** Bed rest and good nursing care when fever is present.

**B Specific Measures** Eliminate causative factors such as chronic systemic infections (e.g., tuberculosis) focal infections and sensitizing drugs. Tetracycline 250 mg q.i.d. for several days may be useful. Corticosteroids may be tried as for erythema nodosum.

**C Local Measures** Treat the stage and type of dermatitis (see p. 53). For acute lesions, employ simple wet dressings and soaks or soothing lotions. For treatment of buccal lesions (see p. 312) Subacute lesions require soothing lotions.

**Prognosis**

The illness usually lasts 2-6 weeks and may recur. The Stevens-Johnson syndrome, a variant of this process (with associated visceral involvement) may be serious or even fatal. The prognosis depends in part on that of the primary disease.

Scott, T. F. M. Hypersensitivity syndromes, erythema multiforme, erythema nodosum, urticaria. *P. Clin North America* 3:771-87, 1956.

**PEMPHIGUS****Essentials of Diagnosis**

- Relapsing symptomatic bullous eruption of skin and mucous membranes
- May appear first on mucous membranes and then on skin in crops or waves
- Acantholysis (Tzanck's test) presumably is diagnostic

Acantholysis is not seen in other bullous eruptions such as erythema multiforme, drug eruptions, contact dermatitis, bullous impetigo, or the less common dermatitis herpetiformis and pemphigoid. All of these diseases have gross clinical characteristics also which distinguish them from pemphigus.

**General Considerations**

Pemphigus is an uncommon skin disease of unknown etiology which is always fatal within 2 months to 5 years if untreated. The bullae appear spontaneously and are relatively asymptomatic, but the complications of the disease lead to great toxicity and debility. There is a surprising lack of pathologic internal medical or laboratory findings; no primary lesions are found in internal organs at biopsy. The disease occurs almost exclusively in adults, and is more common among Jews.

**Clinical Findings**

**A Symptoms and Signs** Pemphigus is characterized by an insidious onset of bullae in crops or waves. The lesions may appear first on the mucous membranes, and these rapidly become erosive. Toxemia and a "mousy odor" may occur soon. Rubbing the thumb on the surface of uninvolved skin may cause easy separation of the epidermis (Nikolsky's sign).

**B Laboratory Findings** On a smear taken from the base of a bulla and stained with Giemsa's stain (Tzanck's test) one may see a unique histologic picture of disruption of the epidermal intercellular connections, called acantholysis. There may be leukocytosis and eosinophilia. As the disease progresses, low serum protein levels may be found as well as serum electrolyte changes. The sedimentation rate may be elevated, and anemia may be present.

**Complications**

Secondary infection commonly occurs often causing extreme debility. Terminally there may be shock, septicemia, disturbances of electrolyte balance, cachexia, toxemia, and pneumonia.

**Treatment**

**A General Measures** Hospitalize the patient at bed rest and provide antibiotics, blood transfusions, and I.V. feedings as indicated. Anesthetic troches may be used before eating to ease painful oral lesions.

**B Specific Measures** Begin therapy with corticotropin I.V. drip, 25 units daily over a period of 5-8 hours, or with large initial doses of corticosteroids, e.g., 100 mg. or more of prednisone (or equivalent). Maintain with repository corticotropin injections or corticosteroids by mouth and reduce dosage as rapidly as possible to a daily minimum maintenance level sufficient to control local or systemic manifestations.

C. Local Measures: Skin and mucous membrane lesions should be treated as for vesicular, bullous, and ulcerative lesions due to any cause (see p. 53). Complicating infection requires appropriate local antibiotic therapy.

#### Prognosis.

Pemphigus was at one time invariably fatal, but the disease can now be controlled indefinitely in most cases. Steroid therapy may induce a complete and permanent remission, in which case maintenance therapy can be discontinued.

Lever, W.F.: Pemphigus. *Medicine* 32:1-114, 1953.

### ATOPIC DERMATITIS (Eczema)

#### Essentials of Diagnosis

- Pruritic, vesicular, exudative, or lichenified eruption on the face, neck, and upper trunk, and the folds of knees and elbows.
- Personal or family history of allergic manifestations.
- Tendency to recur, with remission from age 3 to early youth.

Distinguish from seborrheic dermatitis (frequent scalp involvement, greasy and scaling lesions, and quick response to therapy), contact dermatitis (especially that due to weeds), and lichen simplex chronicus (flat, more circumscribed, duller lesions).

#### General Considerations.

Atopic dermatitis is a chronic superficial inflammation of the skin due to a genetic predisposition to react to allergens (notably wool and animal epidermals) in a particular fashion. It is part of the triad of hay fever-asthma-eczema. The disease usually appears in infancy, disappears at the age of 2 or 3 years, recurs in early youth, and thereafter tends to come and go. Personal or family histories of allergic disease are usually obtained.

#### Clinical Findings.

A. Symptoms and Signs: Itching may be extremely severe and prolonged, leading often to emotional disturbances which have been erroneously interpreted by some as being causative. The distribution of the lesions is

characteristic, with involvement of the face, neck, and upper trunk ("monk's cowl"). The bends of the elbows and knees are involved. An abortive form may involve the hands alone (in which case the history of atopy is all-important). In infants the eruption usually begins on the cheeks and is often vesicular and exudative. In children (and later) it is dry, leathery, and lichenified, although intraepidermal vesicles are occasionally present histologically. Adults generally have dry, leathery, hyperpigmented or hypopigmented lesions in typical distribution.

B. Laboratory Findings: Scratch and intradermal tests are disappointing. Eosinophilia may be present.

#### Treatment.

A. General Measures: Corticotropin or the cortisones may provide spectacular improvement in severe or fulminant eczema (see Chapter 17).

B. Specific Measures: Elimination of inciting agents is, in a sense, the only specific measure. A careful history, trial and error elimination, and exposure technique may be of value in incriminating specific agents. Skin tests are often valueless. Desensitization is of no value. Sensitivities are usually multiple.

The diet should be adequate and well balanced. There is no evidence that standardized or routine dietary restrictions are of value, especially in adults. Trial diets or elimination diets may be of value in determining food allergies in individual cases when an urticarial component is present. Food diaries may be kept by patients with chronic eczema to determine the possibility of food allergy. Reported common food offenders are wheat, milk, eggs, pork, fish, shellfish, tomatoes, strawberries, and chocolate.

Attempts at desensitization by graded injections are disappointing.

An attempt should be made to identify and treat emotional disturbances, but this is of little practical value in the management of the dermatitis.

C. Local Treatment: Avoid all unnecessary local irritations to the skin, such as may occur from excessive bathing or as a result of exposure to irritating drugs, chemicals, greases, and soaps. Soapless detergents are not advisable. Clear up skin infections promptly (particularly those with exudates) by appropriate measures (see Chapter 17). Cortisones in lotion, cream, or ointment form applied sparingly twice daily may be very helpful.

X-ray or grenz ray therapy (by a specialist) may be used effectively, if only temporarily, in many stages

Treat the clinical type and stage of the dermatitis

1 For acute weeping lesions use the solutions listed on p 93 as soothing or astringent soaks, baths, or wet dressings for 30 minutes 3 or 4 times daily. Shake lotions (R 13, 14 p 94) may be employed at night or when wet dressings are not desirable. Lesions on extremities, particularly may be bandaged for protection at night

2 Subacute or subsiding lesions may be treated with shake lotions which may incorporate mild antipruritic or mild stimulating agents. Shake lotions are usually preferred for widespread lesions. Ointments (see p 96) containing mild tar may be used

3 Chronic dry lichenified lesions are best treated with ointments, creams, and pastes (see p 95) containing lubricating, keratolytic, antipruritic and mild keratoplastic agents as indicated. The tars and topical corticosteroids are perhaps the most popular therapeutic agents in chronic eczema (2-5% coal tar in ointments, creams, and pastes). Iodochlorhydroxyquin (Vioform®), 3%, or chlorquinaldol (Sterosan®), ointment or cream may be used in hairy areas or if there is an idiosyncrasy to tar

### Prognosis

The disease runs a chronic course, often with a tendency to disappear and recur

Bier R L Atopic Dermatitis New York Univ Press, 1955

## CIRCULATORY OR STASIS ECZEMA

### Essentials of Diagnosis

- Pruritic, red, weeping, swollen areas of eczema and ulceration on the legs
- Older persons with a history or evidence of varicose veins, trauma, or episodes of thrombophlebitis
- Atrophic pigmented scars of old lesions

Differentiate ulceration from other causes of ulceration of the skin of the legs, e.g., sickle cell anemia, syphilitic ulcers due to the breakdown of a gumma or nodule, and erythema induratum. The eczema itself must

be distinguished from that due to contact dermatitis, e.g., stocking dyes, overtreatment.

### General Considerations.

Eczema of the legs, also called gravitational or hemostatic eczema, is common in older persons, especially men. Most cases are due to impaired circulation, as in varicose veins and other vascular disorders, but the disease may be initiated or made worse by the slightest injury, excessive exposure to soap, medication, cold, low humidity, and even malnutrition. After an injury or reaction to medication in a patch of stasis dermatitis, a generalized pruritic vesicular eruption may occur (autosensitization, "toxic absorption phenomenon"). The reaction may occur spontaneously also.

### Clinical Findings

Severe itching is the only symptom. Red oozing, swollen patches of eczema are present on the backs or outer surfaces of one or both legs (often over the malleoli). Ulcers in the centers of the patches of eczema are rounded and sharply circumscribed, with dirty gray bases and thickened borders. There may be considerable edema. A variant is the hypertensive ischemic ulcer which may be surprisingly painful.

### Treatment.

**A General Measures and Prevention**  
Maintain general health (by proper diet, rest, and sleep) and good skin hygiene. Avoid prolonged sitting, standing, or walking, and constricting garters. Wear properly fitted shoes and stockings.

**B Specific Measures** Treat the underlying specific disease, e.g., varicose veins, obstructive arterial disease amenable to surgery, thrombophlebitis, and congestive heart failure and hypertension.

**C Local Measures** For acute weeping dermatitis use continuous cool wet dressings (see p. 93). Avoid sensitizing or irritating topical medicaments. For infected eczema or ulcers use topical antibiotic powders (Achromycin® surgical powder, Terramycin® topical powder, Neosporin® powder). Combinations of topical corticosteroids with antibiotics in the form of creams, lotions, and ointments may be useful for more chronic processes.

Painting indolent ulcers with Castellani's solution, 1% aqueous gentian violet, or 10% silver nitrate solution may hasten healing.



### Prognosis.

The prognosis depends in great part upon the improvement of the circulation to the limb (e.g., repair of varicose veins) and adequacy of treatment. There is a great tendency toward chronicity and recurrence.

Farber, E.M., & E.E. Batts: Pathologic physiology of stasis syndrome Arch Dermat, 70 653-60, 1954.

## LICREN SIMPLEX CHRONICUS

### Essentials of Diagnosis

- Itching associated with pigmented lichenified skin lesions
- Exaggerated skin lines dividing involved areas into rectangular plaques (lichenification)
- Predisilection for nape of neck, external surfaces of forearms, inner thighs, genitalis, popliteal and cubital folds.

Differentiates from other plaque-like lesions such as lichen planus and nummular eczema. The suboccipital distribution requires differentiation from seborrheic dermatitis.

### General Considerations.

Lichen simplex chronicus is a persistent, usually well localized plaque several cm in diameter, commonly located on the side of the neck, the flexor aspect of the wrist, or the ankle. A "scratch-itch" cycle is a prominent feature. The lesions may arise out of normal skin, or the disease may occur as a complication of contact dermatitis or any irritative dermatitis. It is particularly common in persons of Oriental extraction living in the U.S.A., but is said to be rare in their countries of origin. It is more common in women over 40 years of age.

### Clinical Findings.

Intermittent itching incites the patient to manipulate the lesions. Dry, leathery, hypertrophic, lichenified plaques appear on the neck, wrist, perineum, thigh, or almost anywhere. The patches are well localized and rectangular, with sharp borders, and are thickened and pigmented. The lines of the skin are exaggerated and divide the lesion into rectangular plaques.

### Treatment.

The area should be protected and the patient encouraged to avoid stressful and emotionally charged situations if possible. Topical hydrocortisone cream, 1%, gives relief. The injection of hydrocortisone (or other corticosteroid) suspension into the lesion may occasionally be curative. Roentgen or Grenz radiation may be used conservatively by an expert in the technique.

### Prognosis.

The disease tends to be chronic, and will disappear in one area only to appear in another. Itching may be so intense as to interfere with sleep.

Shaffer, B., & H. Beerman: Lichen simplex chronicus and its variants. A discussion of certain psychodynamic mechanisms and clinical and histopathologic correlations Arch Dermat 64:340-51, 1951

## DERMATITIS MEDICAMENTOSA

### Essentials of Diagnosis

- Abrupt (occasionally delayed) onset of itching and skin lesion after administration of a drug
- Lesion may resemble any inflammatory skin disease but is usually symmetric.
- Constitutional symptoms (malaise, arthralgia, headache, and fever) may be present.

Since the skin lesion may mimic almost any other inflammatory skin disease, this entity must be distinguished (usually on the basis of the history) from all other such lesions.

### General Considerations.

Dermatitis medicamentosa is an acute or chronic inflammatory skin reaction to a drug. Almost any drug, whether ingested, injected, inhaled, or absorbed, may cause a skin reaction. This disorder does not include dermatitis caused by a drug acting locally (dermatitis venenata). The eruption usually recurs upon re-exposure to the same or a related drug, although identical reactions may be produced by unrelated drugs and the same drug may produce different types of reactions in different individuals.

**Clinical Findings**

**A Symptoms and Signs** The onset is usually abrupt with bright erythema and often severe itching, but may be delayed (penicillin, serum). Fever and other constitutional symptoms may be present. The skin reaction usually occurs in symmetric distribution. In a given situation the physician may suspect one (or one of several) specific drugs and must therefore inquire specifically whether it has been used or not.

Drug eruptions may be briefly classified, with examples as follows: (1) erythematous (bismuth arsenicals, barbiturates, sulfonamides, antihistamines, atropine), (2) eczematoid or lichenoid (gold, quinacrine), (3) acneiform or pyodermic (corticotropin, iodides, corticoids, bromides), (4) urticarial (penicillin, antibiotics, sera), (5) bullous (iodides), (6) fixed (phenolphthalein, barbiturates), (7) exfoliative (arsenicals, gold), (8) nodose (sulfathiazole, salicylates). Photosensitization may also occur (phenothiazines, chlorothiazides, demethylchlortetracycline, griseofulvin).

**B Laboratory Findings** The CBC may show leukopenia, agranulocytosis, or evidence of aplastic anemia.

**Complications**

Blood dyscrasias may occur.

**Prevention**

People who have had dermatitis medicamentosa should avoid analogues of known chemical "allergens."

**Treatment**

**A Treat systemic manifestations as they arise** (e.g., anemia, icterus, purpura). Antihistamines may be of value in urticarial and angioneurotic reactions (see p. 68). Corticotropin and cortisones may be indicated for severe cases (see Chapter 17). Calcium gluconate injection, 10%, 10 ml I.V. every other day, may be used instead of corticotropin or the cortisones but is less effective. Do not give more than 3 injections.

**B Specific Measures** Stop all drugs, if possible, and hasten elimination from the body by increasing fluid intake. Dimercaprol (BAL) may be tried in cases due to heavy metals (e.g., arsenic, mercury, gold) (see Chapter 23). Sodium chloride, 5-10 Gm (75-150 gr.) daily orally may hasten elimination of bromides and iodides in cases due to those drugs (see Chapter 23).

**C. Local Measures** Treat the varieties and stages of dermatitis according to the major dermatitis which is simulated.

**Prognosis**

Drug rash usually disappears upon withdrawal of the drug and proper treatment. If systemic involvement is severe (notably with arsenicals), the outcome may be fatal.

Baer, R., & V. H. Witten. Drug eruptions. Pp. 9-37 in Year Book of Dermatology. Year Book, 1960. 61.

Craig, C. H. Drug allergy. In Clinical Immunology and Allergy. Grune & Stratton, 1962.

**EXFOLIATIVE DERMATITIS****Essentials of Diagnosis**

- Scaling and exfoliation of a large area of skin
- Itching, malaise, fever, weight loss
- Primary disease evident or history of exposure to toxic agent (contact, oral, parenteral)

Differentiate from other scaling dermatoses such as psoriasis, lichen planus, and seborrheic dermatitis, which may themselves develop into exfoliative dermatitis.

**General Considerations**

Exfoliative dermatitis, a disorder in which a considerable portion of the skin is reddened and covered with lamellated scales which exfoliate freely, may be due to leukemia or lymphoblastoma, may occur as a sequel to dermatitis medicamentosa or dermatitis venenata, or may be idiopathic.

**Clinical Findings**

**A Symptoms and Signs** Symptoms include itching, weakness, malaise, fever, and weight loss. Exfoliation may be generalized or universal, and sometimes includes loss of hair and nails. Generalized lymphadenopathy may be due to lymphoblastoma or leukemia or may be part of the clinical picture of the skin disease (dermatopathic lymphadenitis). There may be mucosal sloughs.

**B Laboratory Findings** Blood and bone marrow studies and lymph node biopsy may show evidence of leukemia or lymphoblastoma.

Skin biopsy may show evidence of mycosis fungoides. Hypoproteinemias (a grave sign) and anemia may be present.

### Complications

Septicemia, debility (protein loss), pneumonia.

### Prevention

Patients receiving sensitizing drugs should be watched carefully for the development of skin reactions of all types. The drug should be withheld until the nature of the skin reaction is determined. Proved sensitization should be considered an absolute contraindication to further administration of the drug.

### Treatment.

Note: This is a medical emergency.

**A General Measures.** Hospitalize the patient at bed rest with talc on bed sheets. Keep room at warm, constant temperature, and avoid drafts. Transfusions of whole blood or plasma may be required. Avoid all unnecessary medication.

Corticotropin or one of the cortisones may provide spectacular improvement in severe or fulminant exfoliative dermatitis (see Chapter 17). Suitable antibiotic drugs should be given when there is evidence of bacterial infection; pyoderms is the most severe complication of exfoliative dermatitis.

**B Specific Measures.** Stop all drugs if possible, and hasten elimination of offending drug by all means, e.g., by increasing fluid intake. Dimercaprol (BAL) may lessen the severity or duration of reactions due to arsenic or gold (see Chapter 28).

**C Local Measures.** Observe careful skin hygiene and avoid irritating local applications. Treat skin as for acute extensive dermatitis: first with wet dressings, soothing baths (see p. 54), powders (see p. 93), and shake lotions (see p. 94), and later with soothing oily lotions (see p. 93) and ointments (see p. 95).

Topical anti-infective drugs (e.g., 1% aqueous neomycin, oxytetracycline, chlorotetracycline, chloramphenicol, erythromycin or polymyxin B ointment) should be used when necessary (see p. 54).

### Prognosis

The prognosis is variable, depending often upon the prognosis of the primary disease (e.g., lymphoma). Idiopathic exfoliative dermatitis is unpredictable in its duration and recurrence.

Wilson, H T H. Exfoliative dermatitis: its etiology and prognosis. *Arch Dermat* 69: 577-87, 1954.

## DERMATITIS ACTINICA (Erythema Solare or Sunburn)

### Essentials of Diagnosis

- Painful erythema, edema, and vesiculation on sun-exposed surfaces.
- Fever, gastrointestinal symptoms, malaise, or prostration may occur.
- Proteinuria, casts, and hematuria may occur.

Differentiate from contact dermatitis which may develop from one of the many substances in suntan lotions and oils. Sensitivity to actinic rays may also be part of a more serious condition such as porphyria, lupus erythematosus, or pellagra. Phenothiazines, sulfones, chlorothiazides, griseofulvin, and antibiotics may photosensitize the skin.

### General Considerations

Dermatitis actinica is an acute inflammatory skin reaction due to burns resulting from overexposure to sunlight or other sources of actinic rays (cold or hot quartz), photosensitization of the skin by certain drugs or idiosyncrasy to actinic light as seen in some constitutional disorders.

### Clinical Findings

**A Symptoms and Signs.** The acute inflammatory skin reaction is accompanied by pain, fever, gastrointestinal symptoms, malaise, and even prostration. Signs include erythema, edema, and possibly vesiculation and oozing on exposed surfaces. Exfoliation and pigmentary changes often result.

**B Laboratory Findings.** Proteinuria, casts, hematuria, and hemoconcentration may be present.

### Complications

Delayed cumulative effects in fair-skinned people include keratoses and epitheliomas.

### Prevention

Persons with very fair, sensitive skins should avoid prolonged exposure to strong sun or ultraviolet radiation. Preliminary conditioning by graded exposure is advisable.

Protective agents should be applied before exposure, e.g., para-aminobenzoic acid, 10% in hydrophilic ointment; carbolate (phenolized) petrolatum, menthyl anthranilate (5%) and titanium dioxide (5%) cream; or digalloyl trioleate cream (Neo-A-11<sup>®</sup>).

The use of methoxsalen is controversial.

**Treatment**

**A General Measures** Treat constitutional symptoms by appropriate supportive measures. Control pain, fever, and gastrointestinal and other symptoms as they arise.

**B Local Measures** Treat as for any acute dermatitis (see p. 53). First use cooling and soothing wet dressings (see p. 93), and follow with lotions (see p. 94). Greases must be avoided because of their occlusive effect.

**Prognosis**

Dermatitis actinica is usually benign and self-limiting unless the burn is severe or when it occurs as an associated finding in a more serious disorder.

Lamb, J. H. Skin reactions to sunlight.  
New York State J. Med. 59:59-65, 1959.

**LICHEN PLANUS****Essentials of Diagnosis**

- Pruritic, violaceous white-atresked, flat-topped papules.
- Flexor surfaces of wrists, skin of penis, and mucous membranes.
- Usually occurs in an otherwise healthy but emotionally tense person.
- Histopathology is diagnostic.

Distinguish from similar lesions produced by quinacrine or bismuth sensitivity and other papular lesions such as psoriasis, papular eczema, and syphiloderm. Lichen planus on the mucous membranes must be differentiated from leukoplakia. Certain photodeveloping or duplicating solutions may produce contact eruptions which mimic lichen planus.

**General Considerations**

Lichen planus is a chronic inflammatory disease associated with emotional tension or stress. It is more common after the second decade of life and is rare in children.

**Clinical Findings**

Itching is mild to severe. The lesions are violaceous, flat-topped, angulated papules, discrete or in clusters, on the flexor surfaces of the wrists and on the penis, lips, tongue, and buccal and vaginal mucous membranes. The papules may become bulbous or ulcerated. The disease may be generalized. Mucous

membrane lesions have a lacy white network overlying them which is often confused with leukoplakia. Papules are 1-4 mm in diameter with white streaks on the surface (Wickham's striae).

**Treatment**

**A General Measures** Patients are often "high-strung" or tense and nervous, and episodes of dermatitis may follow emotional crises. Measures should be directed at relieving anxiety, e.g., with phenobarbital 15-30 mg (1/4-1/2 gr) 2-4 times daily orally for one month. If chloroquine is not tolerated, hydroxychloroquine sulfate (Plaquenil®), 0.2 Gm b.i.d. orally may be tried for short periods. Corticotropin or cortisones (see Chapter 17) may be required in severe cases.

**B Local Measures** Use shake lotions containing tar (R 16, p. 94). X-ray or Grenz ray therapy (by a specialist) may be used only in severe cases which have proved refractory to other forms of treatment.

**Prognosis**

Lichen planus is a benign disease, but it may persist for months or years and may be recurrent.

Altman J., & H. O. Perry. Variations and course of lichen planus. Arch. Dermat. 84: 179-91, 1961.

Samman P. D. Lichen planus. Practitioner 184:564-71, 1960.

**PSORIASIS****Essentials of Diagnosis**

- Silvery scales on bright red plaques usually on the knees, elbows, and scalp.
- Stippled nails.
- Itching uncommon unless psoriasis is eruptive or occurs in body folds.
- Psoriatic arthritis may be present.
- Histopathology is specific.

Differentiate in the scalp from seborrheic dermatitis, in body folds from intertrigo and moniliasis, and on the nails from onychomycosis.

**General Considerations**

Psoriasis is a common benign, acute or chronic, inflammatory skin disease which apparently is based upon genetic predisposition.

Attempts to incriminate a disturbance in fat metabolism have been unsuccessful. Injury or irritation of a psoriatic skin tends to provoke lesions of psoriasis in the site. Psoriasis occasionally is eruptive, particularly in periods of stress.

### Clinical Findings

There are usually no symptoms. Eruptive psoriasis may itch, and psoriasis in body folds itches severely (inverse psoriasis). The lesions are bright red, sharply outlined plaques covered with silvery scales. The elbows, knees, and scalp are the most common sites. Nail involvement may resemble onychomycosis. Fine stippling in the nails is pathognomonic. There may be associated arthritis which resembles the rheumatoid variety.

### Treatment

**A. General Measures** Warm climates seem to exert a favorable effect. Nonspecific internal medication is of little value with the exception of arsenic, which is hazardous in view of the recurrent nature of the lesions and the delayed effect of excessive use of arsenic (keratoses epithelomas). Fowler's solution (potassium arsenite solution) has been recommended in doses of 3-15 drops twice daily for patients with subacute or chronic lesions although the dosage, duration of administration, indications, and even advisability of using this drug are still controversial subjects. It may be given in repeated courses if indicated, but each course should be continued no longer than 2-3 months. Methotrexate, 2.5 mg orally daily for 6 days (repeated after 3 days' rest) may be tried in severe cases (caution).

Corticotropin or corticosteroids may be necessary to give relief in fulminating cases. Prednisolone U.S.P., 15 mg daily, may be given for 3-7 days.

Reassurance is important since these patients are apt to be discouraged by the difficulties of treatment. An attempt should be made to relieve anxieties.

### B. Local Measures

**1. Acute psoriasis** - Avoid irritating or stimulating drugs. Begin with a shake lotion (Rx 13, 14, p. 94) or bland ointment (see p. 95) containing 5% detergent solution of coal tar. As the lesions become less acute, gradually incorporate mild keratoplastic agents into lotions (see p. 94) and hydrophilic ointments (see p. 95).

**2. Subacute psoriasis** - Give warm baths daily, scrubbing the lesions thoroughly with a brush, soap and water. Apply increasing concentrations of keratoplastic or stimulating

agents incorporated in lotions (see p. 94) and hydrophilic ointments (see p. 95). Solar or ultraviolet irradiations may be applied in gradually increasing doses.

**3. Chronic psoriasis** - Apply ammoniated mercury ointment, 5%, locally b.i.d., or anthralin ointment, 1/4%, locally once a day (avoid the eyes).

Administer the following ultraviolet irradiation and tar regimen daily as needed (modified from Goeckerman). Smear 2-5% coal tar ointment thickly on the skin and leave for 12-24 hours. Wipe off ointment with mineral oil, leaving a light stain. Follow with gradually increasing suberythema doses of ultraviolet light as tolerated.

### Prognosis

Individual manifestations can often be cleared although the tendency to regression and recurrence persists. Psoriasis is a prolonged and recalcitrant disease.

Baer, R. L., & V. H. Witten. Psoriasis: a discussion of selected aspects. Pp. 9-38. In Year Book of Dermatology. Year Book, 1961-62.

Rees, R. B. Psoriasis: recent advances in diagnosis and management. Postgrad Med 26:90-7, 1959.

## PITYRIASIS ROSEA

### Essentials of Diagnosis

- Oval, fawn-colored macules following cleavage lines of the trunk
- Larger herald spot precedes eruption by 1-2 weeks
- Exfoliation of the lesions

Differentiate from syphiloderm, especially when the lesions are numerous and smaller than usual, and from the pityriasis rosea-like variants of dermatophytid, seborrheic dermatitis, and tinea versicolor. Certain drug eruptions (bismuth) may also resemble this disorder.

### General Considerations

Pityriasis rosea is a common mild, non-contagious, acute inflammatory skin disease of unknown etiology. It behaves like an infectious exanthem in that it runs a definite course (usually 6 weeks) and confers a solid 'immunity' (second attacks are rare). It occurs usually during the spring or fall. A chronic

form of the disease occurs rarely. A good tan suppresses the eruption (in the tanned areas only).

### Clinical Findings

Occasionally there is severe itching. The lesions consist of oval, fawn-colored macules 4-5 mm in diameter following cleavage lines on the trunk. Exfoliation of the lesions cause a crinkly scale which begins in the center. The proximal portions of the extremities are involved. A "herald patch" is usually evident.

### Treatment

Acute irritated lesions (uncommon) should be treated as for acute dermatitis with wet dressings (see p. 93) or shake lotions (R 13-16, p. 94). Apply coal tar solution, 5% in starch lotion, b.i.d. Ultraviolet light is helpful.

### Prognosis

Pityriasis rosea is usually an acute self-limiting illness which disappears in about 6 weeks.

Crissey, J. T. Pityriasis rosea. P. Clin North America 3:801-9, 1936.

## SEBORRHEIC DERMATITIS

### Essentials of Diagnosis

- Dry scales or dry yellowish dandruff with or without underlying erythema.
- Scalp, central face, presternal, interscapular areas, umbilicus and body folds.

Distinguish from other skin diseases of the same areas such as intertrigo and fungal infections, and from psoriasis (location).

### General Considerations

Seborrheic dermatitis is an acute or chronic papulosquamous dermatitis. It is based upon a genetic predisposition mediated by an interplay of such factors as hormones, nutrition, infection, and emotional stress.

### Clinical Findings

Pruritus may be present but is an inconsistent finding. The scalp, face, chest, back, umbilicus, and body folds may be oily or dry, with dry scales or oily yellowish scurf. Erythema, fissuring, and secondary infection may be present.

### Treatment

**A General Measures** Prescribe a well-balanced, adequate diet and restrict excess sweets, spices, hot drinks, and alcoholic beverages. Regular working hours, recreation, sleep, and simple cleanliness are recommended. Treat aggravating systemic factors such as infections, overwork, emotional stress, constipation, and dietary abnormalities.

### B Local Measures

- 1 Acute, subacute, or chronic eczematous lesions should be treated as for dermatitis or eczema (see p. 59).
- 2 Seborrhea of the scalp - Use one of the following: (1) Selsun® (selenium sulfide) suspension or Capsebion® once a week after shampoo. Fostex® cream (containing soapless cleansers, wetting agents, hexachlorophene, sulfur, and salicylic acid) may be used as a weekly shampoo for oily seborrhea. (2) Sebulex® is similar to Fostex® and is also effective. Sebizon® lotion (sodium sulfacetamide) should be applied once daily. (3) A mild coal tar scalp lotion (R 20, p. 94) may be used.

3 Seborrhea of nonhairy areas - Mild stimulating lotions (R 18, 19, p. 94), ointment (R 35, p. 96), or 3-5% sulfur in hydrophilic ointment (see p. 96) may be used. (The addition of 1% salicylic acid aids in removing scales.)

4 Seborrhea of intertriginous areas - Avoid greasy ointments. Apply astringent wet dressings (R 1-7, p. 93) followed by 5% ammoniated mercury in hydrophilic ointment (see p. 95).

### Prognosis

The tendency is to life-long persistence. Individual outbreaks may last weeks, months, or years.

Ormaby, O. S., & H. Montgomery. Dermatitis seborrheica. Pp. 1337-45 in Diseases of the Skin. 8th ed. Lea & Febiger, 1954.

## ACNE VULGARIS

### Essentials of Diagnosis

- Pimples (papules or pustules) over the face, back, and shoulders occurring at puberty.
- Cyst formation, slow resolution, scarring.
- The most common of all skin conditions.

Distinguish from acneiform lesions caused by bromides, iodides, and contact with chlorinated naphthalenes and diphenyls

### General Considerations

Acne vulgaris is a common inflammatory skin disease of unknown etiology possibly caused by a genetic predisposition and activated by androgens in the male and progesterone in the female. It may occur at any time from puberty through the period of sex hormone activity. Eunuchs are spared, and the disease may be provoked by giving androgens to a predisposed individual. Identical involvement may occur in identical twins.

The disease is more common in males. Contrary to popular belief, it does not always clear spontaneously when maturity is reached. If untreated, it may persist into the fourth and even sixth decade of life. The skin lesions are the result of sebaceous overactivity, retention of sebum, and abscess formation.

### Clinical Findings

There may be mild soreness, pain or itching, inflammatory papules, pustules, cystic pores, acne cysts, and scarring. The lesions occur mainly over the face, neck, upper chest, back, and shoulders. Comedones are common.

Self-consciousness, embarrassment, and shame may be the most disturbing symptoms.

### Complications

Abscess formation and severe scarring

### Treatment

#### A. General Measures

1. Education of the patient - The patient should be carefully instructed about the nature of his skin disorder, the objectives of treatment, and the necessity for faithful adherence to the treatment program. It should be explained that treatment is essential not only to produce an acceptable cosmetic result while the condition is active but also to prevent permanent scarring.

2. Diet - The diet should be adequate and well-balanced. Forbid chocolate, nuts (including peanut butter), fatty or fried foods, seafoods, alcoholic beverages, spicy foods, and excess carbohydrates. Foods are less important than formerly thought.

3. Eliminate all possible medication especially bromides or iodides.

4. Avoid exposure to mineral oils and greases.

5. Estrogens may be of value in women. They should be stopped for one week prior to

menses each month. Either of the following may be used: (1) Diethylstilbestrol, 0.5-1 mg daily orally, (2) ethinyl estradiol, 0.01-0.05 mg/ml in 70% ethyl alcohol rubbed into the skin twice a day.

6. Treat anemia, malnutrition, infection, gastrointestinal disorders, or other factors which may aggravate acne.

7. Aggravating or complicating emotional disturbances must be taken into consideration and treated appropriately.

8. Tetracycline, 250 mg orally every day, may exert better long-term control than any other treatment in some cases.

B. Local Measures. Ordinary soap is adequate for cleansing, but Phisohex<sup>®</sup> may be used. Avoid greasy cleansing creams and other cosmetics. Shampoo the scalp 1-2 times a week (R 48, p 96). In selected cases, extract blackheads with a comedo extractor after softening the face with warm water compresses for 1/2-1 hour. Incise and drain fluctuant cystic lesions with a small sharp scalpel and apply warm compresses 1/2 hour t.i.d. to promote drainage. Do not incise deeply.

1. Keratoplastic and keratolytic agents - Warm (not steaming) water or boric acid compresses may be used to produce hyperemia and desquamation of lesions. Acne lotion (sulfur-zinc lotion, R 18, p 94) or sulfur-resorcinol lotion (R 19, p 94) may be applied locally to the skin at bedtime and washed off in the morning.

2. Keratolytic ointments and pastes - Begin with weak preparations and increase strength as tolerated. Apply one of the following at bedtime and remove in the morning: (1) Sulfur, 2-10% in hydrophilic ointment (see p 96). (2) Sulfur and kaolin paste (R 38, p 96). (3) Iodochlorhydroxyquin (Vioform<sup>®</sup>) ointment.

3. Commercial preparations for acne include Foster's<sup>®</sup> cream and ointment, Foster's Hc<sup>®</sup> cream, Cort Acne<sup>®</sup> lotion, Rezamid<sup>®</sup> lotion, Acne-Dome<sup>®</sup> cleanser, cream, and lotion, Resulin<sup>®</sup> lotion, Sulfocin<sup>®</sup> cream and lotion, and Ciantis<sup>®</sup> lotion.

4. Dermabrasion - Cosmetic improvement may be achieved by abrasion of inactive acne lesions, particularly flat superficial scars. The skin is first frozen and anesthetized with ethyl chloride or Freon<sup>®</sup> and then carefully abraded with fine sandpaper or special motor-driven abrasive brushes. The technique is not without untoward effects, since hyperpigmentation, grooving, and scarring have been known to occur.

An alternative long-term superficial abrasion utilizes graded abrasive particles of

aluminum oxide incorporated into a soap paste (Brastol<sup>7</sup> Fine, Medium, and Rough) The soap is rubbed well into the involved skin area by the patient and removed with a washcloth and hot water 3 times daily until dryness, redness, and desquamation of the skin occur After a rest period of one month the abrasive soap program is resumed, utilizing the abrasive strength which best suits the individual patient This alternating schedule of abrasive washing may be utilized for several months or years until the desired cosmetic result is achieved

5 Superficial chemosurgery - Liquid phenol or 25-50% trichloroacetic acid applied carefully to acne scars with an applicator and removed immediately with 70% alcohol may produce favorable cosmetic results

6 Irradiation - Simple exposure to sunlight in graded doses is often beneficial Ultraviolet irradiation may be used as an adjunct to other treatment measures Use suberythema doses in graded intervals up to the point of mild erythema and scaling X-ray radiation (by a specialist) should be reserved for the most severe cases after other measures have been tried without success

### Prognosis

Untreated acne vulgaris may persist throughout adulthood and may lead to severe scarring The disease is chronic and tends to recur in spite of treatment

Baer, R L, & V H Witten. Acne vulgaris Remarks on recent advances in knowledge and management Pp 7-32 in Year Book of Dermatology Year Book, 1950-60

## URTICARIA (HIVES)

### &

## ANGIONEUROTIC EDEMA (GIANT HIVES)

### Essentials of Diagnosis

- Wheals with marked itching
- Fever, malaise, and nausea may occur

Distinguish from contact dermatitis, poison oak, and dermatographia

### General Considerations.

Hives is an acute or chronic inflammatory skin reaction of allergic origin. Most acute are caused by ingestion of foods to which the patient is sensitive. Chronic urticaria requires the same sort of exhaustive in-

vestigation indicated for a long-continued unexplained fever. Common causes are foods (shellfish, pork, strawberries, wheat, eggs, milk, tomatoes, chocolate), drugs (antibiotics, salicylates, belladonna, iodides, bromides, serum, vaccines, penolphthalein, opium derivatives), insect bites, parasitic infestation, and emotional disturbances.

### Clinical Findings.

A. Symptoms and Signs In addition to intolerable itching, there may also be malaise and slight fever. Nausea may result from involvement of the gastrointestinal mucosa The wheals vary greatly in size, shape, and amount of swelling

B Laboratory Findings There may be transient blood eosinophilia In chronic urticaria, extensive laboratory investigations may be required in the search for occult foci of infection, food and drug sensitivity, and other possible causes.

### Complications.

Laryngeal obstruction is the most important complication especially in the angioedema variant of urticaria

### Prevention

Avoid re-exposure to sensitizing drugs or foods and aggravating physical, systemic, or emotional factors

### Treatment.

A General Measures Initial castor oil purgation to remove possible antigenic substances has been recommended in acute cases Stools may be examined for parasites During the acute phase the diet should be simple and free of such common offenders as wheat, milk, eggs, pork, fish, shellfish, tomatoes, strawberries, and chocolate The past history, food diaries, trial diets, and elimination diets may be helpful in determining offending foods. The patient should not remain on a restricted diet unless food sensitivity can be demonstrated Avoid unnecessary medication. (Suspect all drugs.)

1 Antihistaminic drugs often give prompt and sustained symptomatic relief

2 Epinephrine injection, 0.3-1 ml of 1:1000 solution, subcut, for acute lesions when laryngeal edema is suspected or present, when urticaria is intense, or when antihistaminic drugs have failed to give relief

3 Ephedrine sulfate, 25 mg (3/8 gr) orally q 4 h, or ephedrine-sedative mixtures

4 Corticotropin or the cortisones (see Chapter 17) may provide spectacular improve-



ment in severe or fulminant angioneurotic edema. These drugs should be used only if it is apparent that the patient will not respond to more conservative measures.

**B. Local Measures:** Topical antipruritic preparations are frequently of benefit (see pp. 54 and 94).

#### Prognosis.

The disease is usually self-limited and lasts only a few days. The chronic form may persist for years.

Kanof, N.B.: *Urticaria*. M Clin North America 43:779-85, 1959

### INTERTRIGO

Intertrigo is caused by the macerating effect of heat, moisture, and friction. It is especially likely to occur in obese persons and in humid climates. Poor hygiene is an important etiologic factor. There is often a history of seborrheic dermatitis. The symptoms are itching, stinging, and burning. The body folds develop fissures, erythema, and sodden epidermis, with superficial denudation. Urine and blood examination may reveal diabetes mellitus, and the skin examination may reveal moniliasis. A direct smear may show abundant cocci.

Treatment is as for *tenia cruris* (see p. 80), but fungicidal agents should not be used. Recurrences are common.

Sulzberger, M.B., Wolf, J., & V H. Witten: *Dermatology. Diagnosis and Treatment*, 2nd ed. Year Book, 1961

### MILIARIA (Heat Rash)

#### Essentials of Diagnosis.

- Burning, itching, superficial aggregated small vesicles or papules on covered areas of the skin.
- Hot moist climate.
- May have fever and even heat prostration.

Distinguish from similar skin manifestations occurring in drug rash.

#### General Considerations.

Miliaria is an acute dermatitis which occurs most commonly on the upper extremities, trunk, and intertriginous areas. A hot, moist environment is the most frequent cause, but individual susceptibility is important and obese persons are most often affected. Plugging of the ostia of sweat ducts occurs, with consequent ballooning and ultimate rupture of the sweat duct, producing an irritating, stinging reaction.

#### Clinical Findings.

The usual symptoms are burning and itching. Fever, heat prostration, and even death may result in severe forms. The lesions consist of small superficial, reddened, thin-walled, discrete but closely aggregated vesicles, papules, or vesicopapules. The reaction occurs most commonly on covered areas of the skin.

#### Prevention

Provide optimal working conditions when possible, i.e., controlled temperature, ventilation, and humidity. Avoid overbathing and the use of strong, irritating soaps. Graded exposure to sunlight or ultraviolet light may benefit persons who will later be subjected to a hot, moist atmosphere. Susceptible persons should avoid exposure to adverse atmospheric conditions.

#### Treatment.

An antipruritic cooling lotion such as the following should be applied 2-4 times daily.

R	Menthol	1.0 (15 gr.)
	Phenol	2.0 (1/2 dr.)
	Glycerin	15.0 (4 dr.)
	Alcohol, 35%, q s. ad	240.0 (8 oz.)

Alternative measures which have been employed with varying success are drying shake lotions (R 13 with 1% phenol, or R 14, p. 94); sulfur-resorcinol lotion (for seborrheic skin) (R 19, p. 94); and antipruritic powders or other dusting powders. Treat secondary infections (superficial pyoderma) with potassium permanganate soaks, compresses, or baths (see p. 93). Ammoniated mercury, 2-5% in hydrophilic ointment (see p. 95), may be employed advantageously. Tannic acid, 10% in 70% alcohol, applied locally b.i.d., serves to toughen the skin.

#### Prognosis.

Miliaria is usually a mild disorder, but death may result in the severe forms (tropical anhidrosis and asthenia) as a result of inter-

ference with the heat-regulating mechanism. The process may also be irreversible to some extent, requiring permanent removal of the individual from the humid or hot climate.

Sulzberger, M B., & F Herrmann. The Clinical Significance of Disturbances in the Delivery of Sweat. Thomas, 1954.

## PRURITUS ANI & VULVAE

### Essentials of Diagnosis

- Itching, chiefly nocturnal, of the anogenital area
- There may be no skin reactions, or inflammation of any degree may occur up to lichenification

Distinguish among the various causes of this condition, such as Candida organisms, parasites, local irritation from contact with drugs and irritants and other primary skin disorders of the genital area such as psoriasis, seborrhea or intertrigo.

### General Considerations

Most cases have no obvious cause, but multiple specific causes have been identified. Anogenital pruritus may be due to the same causes as intertrigo, lichen simplex chronicus, seborrheic dermatitis, dermatitis venenata (from soap, colognes, douches, contraceptives) or may be due to irritating secretions as in diarrhea, leukorrhea, trichomoniasis or local disease (moniliasis, dermatophytosis). Diabetes mellitus must be ruled out. Psoriasis or seborrheic dermatitis may be present. Uncleanliness may be at fault.

### Clinical Findings

**A. Symptoms and Signs.** The only symptom is itching which is chiefly nocturnal. Physical findings are usually not present, but there may be erythema, fissuring, maceration, lichenification, excoriations, or changes suggestive of moniliasis or tinea.

**B. Laboratory Findings.** Urinalysis and blood sugar determination may reveal diabetes mellitus. Direct microscopic examination or culture of tissue scrapings may reveal yeasts, fungi, or parasites. Stool examination may show intestinal parasites.

### Prevention

Treat all possible systemic or local causes. Instruct the patient in proper anogenital hygiene.

### Treatment. (See also Pruritus, p. 54.)

**A. General Measures.** Avoid "hot," spicy foods, and drugs which can irritate the anal mucosa. Treat constipation if present (see p. 304). Instruct the patient to use very soft or moistened tissue or cotton after a bowel movement and to clean thoroughly. Women should apply the same precautions after urinating. Instruct the patient regarding the harmful and pruritus-inducing effects of scratching.

**B. Local Measures.** Hydrocortisone acetate 0.5% and iodochlorhydroxyquin (Vioform®) 1% in an emulsion base applied locally b i d is the treatment of choice. Sitz baths b i d are of value if the area is acutely inflamed and oozing, using silver nitrate 1:10,000-1:200, potassium permanganate 1:10,000 or aluminum subacetate solution 1:20. Underclothing should be changed daily. Paint fissured or ulcerated areas with silver nitrate 5-10%.

X-ray or Grenz ray therapy (by a specialist) may be used if other measures fail.

### Prognosis

Although usually benign, anogenital pruritus may be persistent and recurrent.

Noojin, R O. The dermatologic management of pruritus. South M J 49:149-55, 1956.

## CALLOSITIES & CORNS (OF FEET OR TOES)

Callosities and corns are caused by pressure and friction due to faulty weight-bearing, orthopedic deformities or improperly fitting shoes. Some persons are hereditarily predisposed to excess and abnormal callus formation.

Tenderness on pressure and "after-pain" are the only symptoms. The hyperkeratotic well-localized overgrowths always occur at pressure points. On paring, a glassy core is found (which differentiates these disorders from plantar warts, with multiple bleeding points upon cutting across capillaries). A soft corn often occurs laterally on the proximal portion of the fourth toe as a result of

pressure against the bony structure of the interphalangeal joint of the fifth toe

Treatment consists of correcting mechanical abnormalities which cause friction and pressure. Shoes must be properly fitted, and orthopedic deformities corrected. Callusities may be removed by careful paring of the callus after a warm water soak, or with keratolytic agents, e.g.,

Rx Salicylic acid	4 0 (1 dr )
Acetone	4 0 (1 dr )
Collodion, q s sd	15 0 (1/2 oz )

Sig Apply locally to callus every night and cover with a strip of adhesive. Remove adhesive in the morning. Repeat until corn or callus is removed.

A metatarsal leather bar 1/2 inch wide and 1/4 inch high may be placed on the outside of the shoe just behind the weight-bearing surface of the sole. "Ripple-sole" shoes may be effective.

Women who tend to form calluses and corns should not wear confining footwear.

Andrews, G C. Callus and corns. Pp 561-2 in *Diseases of the Skin*. Saunders, 1954.

## CHRONIC DISCOID LUPUS ERYTHEMATOSUS

### Essentials of Diagnosis

- Red, asymptomatic, localized plaques usually on the face, often in butterfly distribution.
- Scaling, follicular plugging, atrophy, and telangiectasia of involved areas.
- Histology distinctive.

The scales are dry and 'tack-like,' and can thus be distinguished from those of seborrheic dermatitis. Differentiate also from the morphea type of basal cell epithelioma and, by absence of nodules and ulceration, from lupus vulgaris.

### General Considerations

Lupus erythematosus is a superficial, localized discoid inflammation of the skin occurring most frequently in areas exposed to solar or ultraviolet irradiation. The etiology is not known. The disseminated type is discussed in Chapter 25.

### Clinical Findings

**A. Symptoms and Signs.** There are usually no symptoms. The lesions consist of dusky red, well localized, single or multiple plaques, 5-20 mm in diameter, usually on the face and often in a "butterfly pattern" over the nose and cheeks. There is atrophy, telangiectasia, and follicular plugging. The lesion is usually covered by dry, horny, adherent scales.

Ideally a complete medical study should be made to rule out systemic lupus erythematosus.

**B. Laboratory Findings.** There are usually no significant laboratory findings in the chronic discoid type. If there is leukopenia or proteinuria with or without casts, one must suspect the disseminated or systemic form of the disease. Histologic changes are distinctive. The "L E cell" should be sought for in the buffy coat of centrifuged blood when systemic lupus is suspected. Many new variants of this test are now available.

### Complications

Dissemination and scarring may occur.

### Treatment

**A. General Measures.** Treat chronic infections. Provide protection from sunlight and all other powerful radiation. Caution. Do not use any form of radiation therapy.

Maintain optimal general health by well-balanced diet with supplementary vitamins and iron as indicated. Ensure adequate rest and prescribe bed rest when the patient is febrile.

**B. Medical Treatment.** (For discoid type only.) Caution. Any of the following drugs may cause serious eye changes.

1 Quinacrine hydrochloride (Atabrine®) 0.3 Gm (5 gr) orally daily for 2 weeks then 0.1 Gm (1 1/2 gr) daily for 3 months or more. Watch for signs of toxicity.

2 Chloroquine phosphate, 0.5 Gm daily for 1 week, then 0.25 Gm daily. Watch for signs of toxicity.

3 Hydroxychloroquine sulfate (Plaquenil®) 0.2 Gm b.i.d. orally, may occasionally be effective when quinacrine and chloroquine are not tolerated.

4 A triple synthetic antimalarial (Triquin®), 1 tablet b.i.d., may be more effective and better tolerated than the above.

### Prognosis

The disease is persistent but not life-endangering unless it turns into the disseminated variety.

- Leeper R W / M F Allende Antimalarials in the treatment of discoid lupus erythematosus Arch Dermat 73 50 7 1956
- Rebello D J A Ocular reactions to antimalarial drugs Arch Dermat 83 785 1961

## VIRAL INFECTIONS OF THE SKIN

### HERPES SIMPLEX (Cold or Fever Sore)

#### Essentials of Diagnosis

- Recurrent small grouped vesicles especially around oral and genital areas
- May follow minor infections trauma or stress
- Regional lymph nodes may be swollen and tender

Distinguish from other vesicular lesions especially herpes zoster and impetigo In the genital area differentiate from lymphopathic venereum and chancroid

#### General Considerations

Herpes simplex is an acute viral infection Clinical outbreaks which may be recurrent in the same location for years are provoked by fever sunburn indigestion fatigue wind burn menstruation or nervous tension

#### Clinical Findings

The principal symptoms are burning and stinging Neuralgia may precede and accompany attacks The lesions consist of small grouped vesicles which can occur anywhere but which most often occur on the lips mouth and genitals Regional lymph nodes may be swollen and tender

#### Complications

Pyoderma Kaposi's varicelliform eruption (eczema herpeticum or disseminated herpes simplex) encephalitis keratitis

#### Treatment

For persistent or severe recurrent herpes

**A General Measures** Eliminate precipitating agents when possible Routine smallpox vaccination at weekly intervals for 6-8 weeks has been advocated to prevent recurrences but the results are equivocal

**B Local Measures** Dust vesicles twice daily with bismuth formic iodide (BFI) powder or use shake lotions (R 13 14 p 94) camphor spirit locally b i d or epinephrine 1:100 locally b i d Topical cortisones are relatively contraindicated especially for dendritic keratitis The treatment of dendritic keratitis is discussed on p 89

If there is associated cellulitis and lymphadenitis apply cool compresses Treat stomatitis as outlined on p 317 X-ray or Grenz-ray therapy (by a specialist) may be indicated in selected cases

#### Prognosis

Individual attacks last 1-2 weeks Recurrences are common

Baldrige G D Immunologic aspects of herpes simplex herpes zoster and varicella Arch Dermat 79 299 303 1959

### HERPES ZOSTER (Shingles)

#### Essentials of Diagnosis

- Pain along course of nerve followed by painful grouped vesicular lesions
- Involvement is unilateral Lesions are usually on face and trunk
- Swelling of regional lymph nodes (inconstant)

Since poison oak and poison ivy dermatitis may be produced unilaterally and in a streak by a single brush with the plant it must be differentiated at times from herpes zoster Differentiate also from similar lesions of herpes simplex which is usually less painful

#### General Considerations

Herpes zoster is an acute vesicular dermatitis of viral origin There is considerable evidence that this virus and the virus of varicella are identical The 2 diseases may be concurrent

#### Clinical Findings

Pain usually precedes the eruption by 48 hours or more and may persist and actually

increase in intensity after the lesions have disappeared. The lesions consist of grouped, tense, deep-seated vesicles distributed unilaterally along the neural pathways of the trunk. The commonest distributions are on the trunk or face. Regional lymph glands may be tender and swollen.

### Complications

Persistent neuralgia, anesthesia of the affected area following healing, facial or other nerve paralysis, and encephalitis may occur.

### Treatment.

**A General Measures** Barbiturates or bromides may help control tension and nervousness associated with neuralgia. Acetylsalicylic acid or APC compound with or without codeine phosphate, 30 mg ( $\frac{1}{2}$  gr) usually controls pain. Ophthalmologic consultation should be considered for supraorbital involvement to avoid serious ocular complications. Repository corticotropin injection (corticotropin gel), 40-80 units I M daily for 3 days, may relieve the pain.

**B Local Measures** Wet dressings may be necessary for acute and extensive inflammatory lesions (see p. 93). Calamine lotion or other shake lotions (see p. 94) are often of value. Apply the lotion liberally and cover with a protective layer of cotton. Do not use greases.

X-ray therapy (by an expert) may be helpful.

### Prognosis

The eruption persists 2-3 weeks and does not recur. Motor involvement may lead to temporary palsy. Post zoster neuralgia which usually occurs in elderly individuals in supraorbital distribution, is extraordinarily persistent and devastating and does not respond to treatment. Ocular involvement may lead to blindness.

De Moragas, J M., & R R Kierland. The outcome of patients with herpes zoster. Arch Dermat 75 193-6, 1957.

## WARTS

### Essentials of Diagnosis

- Warty elevation anywhere on skin or mucous membranes, usually no larger than 0.5 cm in diameter.
- Prolonged incubation period (average 2-18 months).
- Spontaneous "cures" are frequent (50%) but warts are often unresponsive to any treatment.
- "Recurrences" (new lesions) are frequent.

### General Considerations

Warts are usually seen as solitary or clustered lesions, all presumably due to the same virus, most often on the exposed parts such as the fingers or hands. The incubation period is 2-18 months. No age group is exempt, but warts are perhaps more commonly seen in children and young adults.

### Clinical Findings

There are usually no symptoms. Tenderness on pressure occurs with plantar warts, itching with anogenital warts. Occasionally a wart will produce mechanical obstruction (e.g., nostril, ear canal).

Warts vary widely in shape, size, and appearance. Flat warts are most evident under oblique illumination. Subungual warts may be dry, fissured, and hyperkeratotic, and may resemble hangnails or other nonspecific changes. Plantar warts resemble plantar corns or calluses.

### Prevention

Avoid contact with warts. A person with flat warts should be admonished not to scratch the areas. Occasionally an electric shaver will prevent the spread of warts in razor scratches.

### Treatment.

**A Removal** Remove the warts whenever possible by one of the following means.

1 **Surgical excision** - Inject a small amount of local anesthetic into the base and then remove the wart with a dermal curet or scissors or by shaving off at the base of the wart with a scalpel. Trichloroacetic acid on a tightly wound cotton-tipped applicator may be painted on the wound, or electrocautery may be applied.

2 **Liquid nitrogen** applied with a cotton-tipped applicator until the wart is thoroughly blanched causes after-pain, but large numbers of warts may be so treated bloodlessly.

## 7. Folliculitis

3 Keratolytic agents Either of the following may be used

R Salicylic acid	4 0 (1 dr )
Ethyl aminobenzoate (Benzocaine®)	0 15 (2 1/2 gr )
Acetone	
Flexible collodion aa	15 0 (1/2 oz )

Sig Paint on warts each night

R Salicylic acid	3 6 (1 dr )
Alcohol 40%	
qs ad	120 0 (4 oz )

Sig Paint on flat warts with  
cotton swab daily

B Internal Medical Treatment There is no specific internal remedy Heavy metals such as bismuth and mercury have been used empirically Small children should not be treated with bismuth or mercury internally

### Prognosis

There is a striking tendency to the development of new lesions Warts may disappear spontaneously or may be unresponsive to treatment

Blank H & G Rake Viral and Rickettsial Diseases of the Skin Eye and Mucous Membranes of Man Little Brown 1955

## BACTERIAL INFECTIONS OF THE SKIN

### IMPETIGO

Impetigo is a contagious and auto inoculable infection of the skin caused by staphylococci or less commonly streptococci The infected material may be transmitted to the skin by dirty fingernails In children the source of infection is often a pyogenic nasal infection or another infected child In men the barber shop is a common source of infection

Itching is the only symptom The lesions consist of macules vesicles pustules and honey colored gummy crusts which when removed leave denuded red areas The face and other exposed parts are most often involved

Impetigo must be distinguished from other vesicular and pustular lesions such as herpes

simplex varicella and contact dermatitis (dermatitis venenata)

Treatment is as for folliculitis Response to local treatment for infection and often to antibiotics is usually good The nephritis which occasionally develops may be fatal (particularly in infants)

McCarthy J T & C T Nelson Common bacterial infections of the skin P Clin North America 3 499 518 1956

### ECTHYMA

Ecthyma is a deeper form of impetigo with ulceration It occurs frequently on the legs and other covered areas often as a complication of debility and infestations

### BOCKHART'S IMPETIGO

Bockhart's impetigo is a staphylococcal infection which produces tense globular painful pustules at the follicular orifices It is a form of folliculitis (see below)

### IMPETIGO NEONATORUM

Impetigo neonatorum is a highly contagious potentially serious form of impetigo occurring in infants It requires prompt systemic treatment and protection of other infants (isolation excluding from the nursery of personnel with pyoderma etc ) The lesions are bullous and massive and accompanied by systemic toxicity Death may occur

### FOLLICULITIS

(Including Sycosis Vulgaris or Barber's Itch)

### Essentials of Diagnosis

- Itching and burning in hairy areas
- Pustules in the hair follicles
- In sycosis inflammation of surrounding skin area

Differentiate from acne vulgaris and infections of the skin such as impetigo

### General Considerations.

Folliculitis is caused by staphylococcal infection of a hair follicle. When the lesion is deep-seated, chronic, and recalcitrant, it is called sycosis. Sycosis is usually propagated by the auto-inoculation and trauma of shaving. The upper lip is particularly susceptible to involvement in men who suffer with chronic nasal discharge from sinusitis or hay fever.

### Clinical Findings.

The symptoms are slight burning and itching, and pain on manipulation of the hair. The lesions consist of pustules of the hair follicles. In sycosis the surrounding skin becomes involved also and so resembles eczema, with redness and crusting.

### Complications

Abscess formation

### Prevention

Correct precipitating or aggravating factors: systemic (e.g., diabetes mellitus) or local causes (e.g., mechanical or chemical skin irritations, discharges).

### Treatment.

**A. Specific Measures** Systemic anti-infectives may be tried if the skin infection is resistant to local treatment, if it is extensive or severe and accompanied by a febrile reaction, if it is complicated, or if it involves the so-called "danger areas" (upper lip, nose, and eyes).

Local anti-infective agents are of proved value and should be tried in sequence until a favorable response is obtained (allowing 3-4 days for evaluation). They should be applied initially at night and protected by dressings, soaks should be applied during the day. After the area has cleared, any of the following preparations may be applied 2-4 times daily: (1) Neomycin sulfate, 0.1% in water, locally q.i.d. (2) Iodochlorhydroxyquin (Vioform®), 3% in cream or ointment form, locally b.i.d. (3) Other antibiotics, alone or in combination, as ointments locally 2-4 times daily. These include polymyxin B in combination with bacitracin or oxytetracycline, neomycin, chloramphenicol, and erythromycin.

Penicillin and sulfonamides should not be used in ointment form.

**B. Local Measures** Cleanse the area gently with a weak soap solution and apply soaks or compresses to the involved area for 15 minutes b.i.d. (see p. 93). When skin is softened, gently open the larger pustules and trim away necrotic tissue.

### Prognosis

Folliculitis is often stubborn and persistent, lasting for months and even years.

Lerner, M. R., & A. B. Lerner: *Dermatologic Medications*, 2nd ed. Year Book, 1960.

## FURUNCULOSIS (BOILS) & CARBUNCLES

### Essentials of Diagnosis

- Extremely painful inflammatory swelling of a hair follicle which forms an abscess
- Primary predisposing debilitating disease sometimes present
- Antibiotic-resistant strains of "hospital staph" are responsible for an increasing percentage of cases

Differentiate from deep mycotic infections such as sporotrichosis and blastomycosis, and other bacterial infections such as anthrax, tularemia, and from acne cysts.

### General Considerations.

A furuncle (boil) is a deep-seated infection (abscess) involving the entire hair follicle and adjacent subcutaneous tissue. The most common sites of occurrence are the hairy parts exposed to irritation and friction, pressure, or moisture, or to the plugging action of petroleum products. Because the lesions are auto-inoculable they are often multiple. Thorough investigation usually fails to uncover a predisposing cause, although on occasions a patient may have uncontrolled diabetes mellitus, nephritis, or other debilitating disease.

A carbuncle is several furuncles developing in adjoining hair follicles and coalescing to form a conglomerate, deeply situated mass with multiple drainage points.

### Clinical Findings

**A. Symptoms and Signs** The extreme tenderness and pain are due to pressure on nerve endings, particularly in areas where there is little room for swelling of underlying structures. The pain, fever, and malaise are more severe in carbuncles than with furuncles. The follicular abscess is either rounded or conical. It gradually enlarges, becomes fluctuant, and then softens and opens spontaneously after a few days to 1-2 weeks to discharge a core of necrotic tissue and pus. The inflam-

mation occasionally subsides before necrosis occurs

A carbuncle is much larger than a boil. Instead of having only one core it has 2 or more.

**B Laboratory Findings** There may be slight leukocytosis.

### Complications

Fatal cavernous sinus thrombosis may occur as a complication of a manipulated furuncle on the central portion of the upper lip or near the nasolabial folds. Perinephric abscess, osteomyelitis, and other hematogenous staphylococcal infections may also occur.

### Treatment.

**A Specific Measures** Systemic anti-infective agents are indicated (chosen on the basis of cultures and sensitivity tests) only if lesions are severe, extensive, or complicated or located in danger areas (around the neck and head).

**B Local Measures** Immobilize the part and avoid overmanipulation of inflamed areas. Use moist or dry heat to help larger lesions "localize." Use proper surgical incision, debridement or debridement after the lesions are "mature." Do not incise deeply. Apply anti-infective ointment and bandage the area loosely during drainage.

### Prognosis

Recurrent crops may harass the patient for months or years. Carbunculosis is more severe and more hazardous than furunculosis.

Suizberger, M B., & R L. Baer. Treatment of pyodermas (common pus-forming infections of the skin). Pp 9-52 in Year Book of Dermatology and Syphilology. Year Book, 1950.

## ERYSIPELAS

### Essentials of Diagnosis

- Edematous, spreading, circumscribed, hot, erythematous area, with or without vesicle or bulla formation.
- Pain, malaise, chills and fever.
- Leukocytosis, increased sedimentation rate.

Distinguish from cellulitis, with its less definite margin and involve-

ment of deeper tissues, and from erysipeloid, a benign bacillus infection producing redness of the skin of the fingers or the backs of the hands in fishermen and meat handlers.

### General Considerations.

Erysipelas is an acute inflammation of the skin and subcutaneous tissue caused by infection with beta-hemolytic streptococci. It occurs classically on the cheek.

### Clinical Findings

**A Symptoms and Signs** The symptoms are pain, malaise, chills, and moderate fever. A bright red spot appears first, very often near a fissure at the angle of the nose. This spreads to form a tense, sharply demarcated, glistening, smooth, hot area. The margin characteristically makes noticeable advances from day to day. The patch is somewhat edematous and can be pitted slightly with the finger. Vesicles or bullae occasionally develop on the surface. The patch does not usually become pustular or gangrenous, and heals without scar formation. The disease may complicate any break in the skin which provides a portal of entry for the organism.

**B Laboratory Findings** Leukocytosis and increased sedimentation rate almost invariably occur.

### Complications

Unless erysipelas is promptly treated, death may result from extension of the process and systemic toxicity, particularly in the very young and in the aged.

### Treatment.

Place the patient at bed rest with the head of his bed elevated, apply hot packs, and give acetylsalicylic acid for pain and fever. Penicillin is specific for beta-hemolytic streptococcal infections.

### Prognosis

Erysipelas formerly was very dangerous to life, particularly in the very young and in the aged. With antibiotic therapy the disease can now usually be quickly controlled. Prompt and adequate treatment usually will limit it to one attack.

McCarthy, J. T., & C. T. Nelson. Common bacterial infections of the skin. P. Clin North America 3:499-518, 1956.



## CELLULITIS

Cellulitis, a diffuse spreading infection of the skin, must be differentiated from erysipelas (a superficial form of cellulitis) because the two conditions are quite similar. Cellulitis involves deeper tissues and may be due to one of several organisms, usually cocci. The lesion is hot and red but has a more diffuse border than does erysipelas. Cellulitis usually occurs after a break in the skin. Recurrent attacks may sometimes affect lymphatic vessels, producing a permanent swelling called "solid edema."

The response to systemic anti-infective measures (penicillin, broad-spectrum antibiotics, or sulfonamides) is usually prompt and satisfactory.

## ERYSIPELOID

Erysipelothrix rhusiopathiae infection must be differentiated from erysipelas and cellulitis. It is a benign infection usually seen in fishermen and meat handlers, which is characterized by redness of the skin, most often of a finger or the back of the hand, and which gradually extends over a period of several days. Systemic involvement which occurs rarely, is manifested by reversal of the albumin-globulin ratio and other serious changes.

Penicillin is usually promptly curative. Broad-spectrum antibiotics may be used instead.

Nelson, E. • Five hundred cases of erysipeloid  
Rocky Mountain M J 52 40-2, 1955

## DECUBITUS ULCERS (Bedsore)

Bedsore (pressure sores) are a special type of ulcer caused by impaired blood supply and tissue nutrition due to prolonged pressure over bony prominences. The skin overlying the sacrum and hips is most commonly involved, but bedsore may also be seen over the occiput, elbows, heels, and ankles. They occur most readily in aged, paralyzed, and debilitated patients in whom an adequate underlying fat pad is lacking. Low-grade infection may occur.

Good nursing care and nutrition and maintenance of skin hygiene are important preventive measures. The skin and the bed linens should be kept clean and dry. Bedfast, paralyzed, moribund or listless patients who are candidates for the development of decubiti must be turned frequently (at least every hour) and must be examined at pressure points for the appearance of small areas of redness and tenderness. Inflated rubber rings, rubber pillows, and an alternating pressure mattress all of which are essential in the treatment of early lesions are of value also in prevention.

Early lesions should also be treated with topical antibiotic powders and adhesive absorbent bandage (Gelfoam®). Established lesions require surgical consultation and care. A sheepskin (obtainable from the California Woolgrowers Association) on the bed with the wool next to the skin may work best in some cases. It may be laundered often.

Breck, L. W., & S. Gonzalez. Sheepskins to prevent decubitus ulcers. Clin Orthop 21 235-7, 1962

Weiss, A. A. Management of decubitus ulcers. New York State J Med 60 79-82, 1960

## FUNGAL INFECTIONS OF THE SKIN

Mycotic infections are traditionally divided into 2 principal groups: superficial and deep. In this chapter we will discuss only the superficial infections: tinea capitis, tinea corporis, and tinea cruris, dermatophytosis of the feet and dermatophytid of the hands, tinea unguis (onychomycosis, or fungal infection of the nails), and tinea versicolor. Candidiasis belongs in an intermediate group but will be considered here as well as with the deep mycoses.

The diagnosis of fungous infections of the skin is usually based on the location and characteristics of the lesions and on the following laboratory examinations: (1) Direct demonstration of fungi in 10% potassium hydroxide preparations of scrapings from suspected lesions. (2) Cultures of organisms. (3) Skin tests, e.g., trichophytin (not reliable) for superficial mycoses. (This test has exclusion value in suspected dermatophytid.) (4) Examination with Wood's light (an ultraviolet light with a special filter), which causes hairs to fluoresce a brilliant green when they are infected by Microsporum organisms (cause about 90% of cases of tinea capitis in some areas of the U.S.A.). The lamp is also invaluable in

following the progress of treatment. Ringworm of the scalp may be totally unsuspected yet discovered easily with Wood's light in mass surveys of school children. Trichophyton-infected hairs do not fluoresce. (5) Histologic sections stained with periodic acid [Schiff (Hotchkiss-McManus)] technic. Fungal elements stain red and are easily found.

Serologic tests are of no value in the diagnosis of superficial fungal infections.

#### Principles of Local Treatment

Treat acute active fungal infections initially for any acute dermatitis (see p. 53). Note: It may be necessary to treat the dermatitis before applying topical fungicidal medication.

Most topical fungicidal agents are strong skin irritants. It is easy to overtreat.

#### General Measures and Prevention

Keep the skin dry, since moist skin favors the growth of fungi. A cool climate is preferred. Reduce exercise and activities to prevent excessive perspiration. Dry the skin carefully after bathing or after perspiring heavily. Socks and other clothing should be changed often. Sandals or open-toed shoes should be worn. Skin secretions should be controlled with talc or other drying powders or with drying soaks (see p. 93). Sedatives (e.g., phenobarbital) may be effective in reducing skin secretions in tense, nervous people. Toughen the skin with graded daily sun baths or with a quartz lamp.

Lewis, G. M., & others. An Introduction to Medical Mycology Year Book 1958.

#### Griseofulvin (Grifulvin<sup>®</sup>, Fulvicin<sup>®</sup>)

Griseofulvin is an antibiotic obtained by fermentation of several species of penicillia. It is water-soluble and thermostable and is not related chemically to any other antibiotic in current use. Cross-sensitization with other antibiotics has not been a problem. The drug is deposited in keratinous structures and apparently acts by interfering with reproduction of the fungal elements.

Griseofulvin is employed in oral dosage against dermatophyte or 'ringworm' fungal infections. It is most effective for ringworm infections of the scalp and quite effective for involvement of the face, neck, and trunk, reasonably effective against ringworm of the groin, and less effective for involvement of hands and feet. Nail infections are least responsive to griseofulvin therapy.

The drug is supplied in tablets of 250 and 500 mg. The average daily dose is 1 Gm.

orally for adults and comparably less for children. A total of 3 Gm. in one oral dose will cure most cases of ringworm of the scalp in children. Prolonged treatment may be required for onychomycosis.

Toxic reactions include headache, urticaria, dizziness, drowsiness, morbilliform and hemorrhagic eruptions, gastrointestinal distress and loose stools. Although severe reactions are occasionally reported, hematologic studies and assays of kidney and liver function have shown the drug to be essentially free of severe side reactions.

International symposium sponsored by University of Miami, October 26-27, 1959.

Griseofulvin and dermatomycoses. Arch. Dermat. 81: 649-682, 1960.

#### TINEA CAPITIS (Ringworm of Scalp)

##### Essentials of Diagnosis

- Round gray scaly "bald" patches on the scalp
- Usually in prepubertal children
- Often fluorescent under Wood's lamp
- Microscopic examination or culture identifies the fungus

Differentiate from other diseases of scalp hair such as pediculosis capitis, pyoderma, alopecia areata, and trichotillomania (voluntary pulling out of one's own hair).

##### General Considerations

This persistent, contagious and sometimes epidemic infection occurs almost exclusively in children and disappears spontaneously at puberty. Two genera (*Microsporum* and *Trichophyton*) cause ringworm infections of the scalp. *Microsporum* accounts for many of the infections and hairs infected with this genus fluoresce brilliantly under Wood's light. *Trichophyton* species account for some of the very resistant infections which may persist into adulthood.

##### Clinical Findings

**A. Symptoms and Signs.** There are usually no symptoms although there may be slight itching. The lesions are round, gray, scaly, apparently bald patches on the scalp (the hairs are broken off and the patches are not actually bald). Scalp ringworm may be undetectable with the naked eye, becoming

visible only under the Wood's light, in which case the hairs exhibit a brilliant green fluorescence extending down into the hair follicle

**B Laboratory Findings** Microscopic or culture demonstration of the organisms in the hairs may be necessary.

#### Prevention

Exchange of headgear must be avoided, and infected individuals or household pets must be vigorously treated and re-examined for determination of cure. The scalp should be washed after haircuts.

#### Complications

Kerion is the only complication.

#### Treatment

Griseofulvin (Grifulvin<sup>®</sup>, Fulvicin<sup>®</sup>), 0.25-0.5 Gm by mouth daily or twice daily for 2 weeks, will cure most cases.

#### Prognosis

Tinea capitis may be very persistent but usually clears spontaneously at puberty. Most ringworm infections of the scalp will clear spontaneously in 1-2 years even if not treated.

Kligman, A. M. Tinea capitis due to *M. audouinii* and *M. canis*. Arch Dermat 71:313-36, 1955

### TINEA CORPORIS OR TINEA CIRCINATA (Body Ringworm)

#### Essentials of Diagnosis

- Pruritic, ringed, scaling, centrally clearing lesions, small vesicles in a peripherally advancing border
- On exposed skin surfaces
- History of exposure to infected domestic animal
- Laboratory examination by microscope or culture confirms diagnosis

Itching distinguishes tinea corporis from other skin lesions with annular configuration, such as the annular lesions of psoriasis, erythema multiforme, and pityriasis rosea.

#### General Considerations

The lesions are often on exposed areas of the body such as the face and arms. A history of exposure to an infected cat may be obtained. All species of dermatophytes may cause this disease, but some are more common than others.

#### Clinical Findings.

**A Symptoms and Signs** Itching is usually intense, which serves to distinguish the disease from other ringed lesions. The lesions consist of rings of vesicles with central clearing, grouped in clusters and distributed asymmetrically, usually on an exposed surface.

**B Laboratory Findings** Hyphae can be demonstrated readily by removing the cap of a vesicle and examining it microscopically in a drop of 10% potassium hydroxide. The diagnosis may be confirmed by culture.

#### Complications

Complications include extension of the disease to the scalp hair or nails (in which case it becomes much more difficult to cure), overtreatment dermatitis, pyoderma, and dermatophytid.

#### Prevention (See also p. 78)

Avoid contact with infected household pets and avoid exchange of clothing without adequate laundering.

#### Treatment

**A Specific Measures** Griseofulvin (Grifulvin<sup>®</sup>, Fulvicin<sup>®</sup>) 0.5 Gm orally daily for children and 1 Gm orally daily for adults.

**B Local Measures** Caution. Do not over-treat.

R Salicylic acid	0.3 (5 gr)
Sulfur, ppt	0.9 (15 gr)
Hydrophilic ointment	
q s ad	30.0 (1 oz)

Sig Apply locally b i d

Compound undecylenic acid ointment may be used in the less chronic and nonthickened lesions.

#### Prognosis

Body ringworm usually responds promptly to griseofulvin by mouth or to conservative topical therapy.

Ferguson, E. H., & S. Rothman. Fungus infections of the skin. P Clin North America 3:555-95, 1956

## TINEA CRURIS (Jock Itch)

### Essentials of Diagnosis

- Marked itching in intertriginous areas
- Peripherally spreading sharply demarcated centrally clearing erythematous macular lesions with or without vesicle formation
- May have associated tinea infection of feet
- Laboratory examination with microscope or culture confirms diagnosis

Differentiate from other lesions involving the intertriginous areas such as moniliasis, seborrheic dermatitis, intertrigo, and psoriasis of body folds (inverse psoriasis).

### General Considerations

Tinea cruris lesions are confined to the groin and gluteal cleft and are as a rule more indolent than those of tinea corporis and tinea circinata. The disease often occurs in athletes as well as in persons who are obese or who perspire a great deal. Any of the dermatophytes may cause tinea cruris and it may be transmitted to the groin from active dermatophytosis of the foot. Intractable pruritus and may occasionally be caused by tinea infection.

### Clinical Findings

**A Symptoms and Signs** Itching is usually more severe than that which occurs in seborrheic dermatitis or intertrigo. Inverse psoriasis, however, may itch even more than tinea cruris. The lesions consist of erythematous macules with sharp margins, cleared centers and active spreading peripheries in intertriginous areas. There may be vesicle formation at the borders and satellite vesicular lesions are sometimes present.

**B Laboratory Findings** Hyphae can be demonstrated microscopically in 10% potassium hydroxide preparations. The organism may be cultured readily.

### Treatment

**A General Measures** (See also p 53) Drying powder (see p 93) should be dusted into the involved area 2-3 times a day, especially when perspiration is excessive. Keep the area clean and dry but avoid overbathing. Prevent intertrigo or chafing by avoiding over-treatment which predisposes to further infection and complications. Rough-textured clothing should be avoided.

**B Specific Measures** Griseofulvin (see p 78) is indicated for severe cases. Give 1 Gm orally daily for 1-2 weeks.

**C Local Measures** Treat the stage of dermatosis (see p 53). Secondarily infected or inflamed lesions are best treated with soothing and drying solutions with the patient at bed rest. Use wet compresses of potassium permanganate 1:10,000 (or 1:20 aluminum acetate solution) or, in case of anogenital infection, sitz baths.

**Fungicidal preparations** Any of the following may be used: (1) Sulfur-resorcinol lotion b.i.d. (R 19, p 94). (2) Weak solutions of iodine (not more than 1% tincture) b.i.d. (3) Carbolfuchsin solution (Castellani's paint) one third strength once a day. (4) Compound undecylenic acid ointment b.i.d. (5) Sulfur-salicylic acid ointment (R 34, p 96).

### Prognosis

Tinea cruris usually responds promptly to topical or systemic treatment.

Blank F & H Prichard. Epidemic ringworm of the groin. Arch Dermat 85:410 11 1962.

## DERMATOPHYTOSIS (Tinea of Palms & Soles, 'Athlete's Foot')

### Essentials of Diagnosis

- Itching, burning, and stinging of interdigital webs, palms and soles
- Deep vesicles in acute stage
- Exfoliation, fissuring, and maceration in subacute or chronic stages
- Skin scrapings examined microscopically or by culture may reveal fungus

Differentiate from other skin diseases involving the same areas such as contact dermatitis (from footwear powders, nail polish), moniliasis and scabies.

### General Considerations

Dermatophytosis is an extremely common acute or chronic dermatosis. It is possible that the causative organisms are present on the feet of most adults at all times. Certain individuals appear to be more susceptible than others. Most infections are caused by Trichophyton and Epidermophyton species.

## Clinical Findings

**A Symptoms and Signs** The presenting symptom is usually itching. However, there may be burning, stinging, and other sensations, or frank pain from secondary infection with complicating cellulitis, lymphangitis, and lymphadenitis. Dermatophytosis often appears as a fissuring of the toe webs, perhaps with denudation and sodden maceration. However, there may also be grouped vesicles distributed anywhere on the soles or the palms, a generalized exfoliation of the skin of the soles, or destructive nail involvement in the form of discoloration and hypertrophy of the nail substance with pithy changes. Acute reddened, weeping vesicular lesions are seen on the skin in the acute stages.

**B Laboratory Findings** Hyphae can often be demonstrated microscopically in skin scales treated with 10% potassium hydroxide. Culture with Sabouraud's medium is simple and often informative, but does not always demonstrate pathogenic fungi.

## Prevention

The essential factor in prevention is personal hygiene. Rubber or wooden sandals should be used in community showers and bathing places. Open-toed shoes and sandals are best for general wear. Careful drying between the toes after showering is recommended. Socks should be changed frequently. Apply dusting and drying powders p r n (see p 93), and place small wads of cotton between the toes at night.

## Treatment

**A Specific Measures** Griseofulvin (see p 78) has been disappointing in the treatment of dermatophytosis of the feet and should be used only for severe cases or those which are recalcitrant to topical therapy.

**B Local Measures** Caution. Do not over-treat.

1 Acute stage (lasts 1-10 days) - Give aluminum subacetate solution soaks (R 4 p 93) for 20 minutes 2-3 times daily. If secondary infection is present, use soaks of 1:10,000 potassium permanganate. If secondary infection is severe or complicated, treat as described on p 53.

2 Subacute stage - Any of the following may be used: (1) Zincundecate ointment b i d (2) Whitfield's ointment 1/4-1/2 strength (R 33 p 96) (3) Solution of coal tar, 5% in starch lotion, or R 16 p 94 (4) Coal tar 1-2% in Lassar's paste.

3 Chronic stage - Use any of the following: (1) Iodine as 0.1-1% tincture painted on affected areas once daily (2) Whitfield's ointment 1/4-1/2 strength (R 33, p 96) (3) Compound undecylenic acid ointment b i d (4) Alcoholic Whitfield's solution (R 46 p 96) (5) Carbol-fuchsin solution (Castellani's paint).

**C Mechanical Measures** Carefully remove or debride dead or thickened tissues after soaks or baths.

**D X-ray or Grenz ray therapy** (by a specialist) may be of value when other measures fail.

## Prognosis

Dermatophytosis usually responds well to treatment, but recurrences are common in strongly predisposed persons.

**Sulzberger M B & R L Baer** Some recent advances in dermatologic mycology: tinea pedis, Trichophyton rubrum infections, tinea capitis, moniliasis. Pp 7-33 in Year Book of Dermatology and Syphilology, Year Book, 1954-55.

## DERMATOPHYTID

(Allergy or Sensitivity to Fungi)

## Essentials of Diagnosis

- Pruritic grouped vesicular lesions involving the sides and flexor aspects of the fingers and the palms
- Fungal infection elsewhere on body usually the feet
- Trichophyton skin test positive. No fungus demonstrable in lesions

Differentiate from all diseases causing vesicular eruptions of the hands, especially contact dermatitis, dyshidrosis, and localized forms of atopic dermatitis.

## General Considerations

Dermatophytid is a sensitivity reaction to an active focus of dermatophytosis elsewhere on the body, usually the feet. Fungi are present in the primary lesion but are not present in the lesions of dermatophytid. The hands are most often affected, but dermatophytid may occur on other areas of the body also.

## Clinical Findings

**A Symptoms and Signs** Itching is the only symptom. The lesions consist of grouped

vesicles, often involving the thenar and hypothenar eminences. Lesions are round, up to 15 mm in diameter and may be present on the sides and flexor aspects of the fingers. Lesions occasionally involve the backs of the hands or may even be generalized.

**B Laboratory Findings** The trichophyton skin test is positive but it may also be positive with other disorders. A negative trichophyton test rules out dermatophytid. Repeated negative microscopic examinations of material taken from the lesions is necessary before the diagnosis of dermatophytid can be established.

#### Prevention

Treat fungal infections early and adequately and prevent recurrences (see p 78).

#### Treatment

General measures are as outlined on p 53. The lesions should be treated according to type of dermatitis. The primary focus should be treated with griseofulvin (see p 78) or by local measures as described for dermatophytosis (see p 80).

#### Prognosis

Dermatophytid may occur in an explosive series of episodes and recurrences are not uncommon however it clears with adequate treatment of the primary infection elsewhere on the body.

Wilson J W. Clinical and Immunologic Aspects of Fungous Diseases. Thomas 1967.

## TINEA UNGULUM & CANDIDAL ONYCHOMYCOSIS

#### Essentials of Diagnosis

- Lusterless, brittle, hypertrophic, friable nails.
- Fungus demonstrated in nail section by microscope or culture.

Distinguish from nail changes caused by contact with strong alkalis and certain other chemicals and from those due to psoriasis, lichen planus and candidiasis.

#### General Considerations

Tinea unguinum is a destructive Trichophyton or Fp dermatophyton infection of one or more (but rarely all) fingernails or toenails. The species most commonly found are Tri-

chophyton mentagrophytes, T. rubrum, and Epidermophyton floccosum. Candida albicans causes candidal onychomycosis.

#### Clinical Findings

**A Symptoms and Signs** There are usually no symptoms. The nails are lusterless, brittle, and hypertrophic, and the substance of the nail is friable and even pithy. Irregular segments of the diseased nail may be broken.

**B Laboratory Findings** Laboratory diagnosis is mandatory. Portions of the nail should be cleared with 10% potassium hydroxide and examined under the microscope for branching hyphae or collections of spores. Fungi may also be cultured using Sabouraud's medium. Periodic acid-Schiff stain of a histologic section will also demonstrate the fungus readily.

#### Treatment

**A General Measures** See p 53.

**B Specific Measures** Griseofulvin (see p 78) in full dosage daily for 3-6 months may be necessary for tinea unguinum, and even this may not result in cure. Candida infection may be treated specifically with nystatin (Mycostatin<sup>®</sup>) cream or powder, or amphotericin B (Fungizone<sup>®</sup>) lotion.

**C Local Measures** Sandpaper or file the nails daily (down to nail bed if necessary). Surgical avulsion of the nail may be required. **Fungicidal agents** Apply one of the following on affected nails: (1) Iodine tincture, 0.1-1%, b i d. (2) Chrysarobin 4%, in chloroform b i d. (3) Chrysarobin, 0.1-0.5% in petrolatum b i d. (4) Whitfield's ointment, half-strength, b i d. (5) Diamthazole dihydrochloride (Astero<sup>®</sup>) ointment, 5%, locally b i d. (6) Verdefam<sup>®</sup> liquid (sodium propionate, sodium caprylate, propionic acid, undecylenic acid, salicylic acid, copper undecylenate), b i d.

X-ray in fractional doses (by a specialist) may be of aid in mild cases and may require months for cure. Some authorities feel that x-ray has no place in the treatment of onychomycosis.

#### Prognosis

Some authorities feel that tinea unguinum cannot be cured. Treatment must be conscientious and prolonged. Griseofulvin by mouth may be curative, but relapses are common.

Vilanova, X., Casanovas, M., & J. Francino:  
Onychomycosis, an experimental study.  
J. invest. Dermat. 27:77-100, 1956.

## TINEA VERSICOLOR

### Essentials of Diagnosis.

- Skin areas which will not tan
- Velvety, chamois-colored macules which scale with scraping
- Trunk distribution the most frequent site
- Fungus on microscopic examination of scales.

Distinguish from vitiligo on basis of appearance. Differentiate also from seborrheic dermatitis of the same areas.

### General Considerations.

Tinea versicolor is a mild, superficial *Malassezia furfur* infection of the skin (usually of the trunk). The eruption is called to the patient's attention by the fact that the involved areas will not tan, and the resulting pseudochromia may be mistaken for vitiligo. The disease is not particularly contagious and is apt to occur more frequently in those who wear heavy clothing and who perspire a great deal.

### Clinical Findings.

**A. Symptoms and Signs** There may be mild itching. The lesions are velvety, chamois-colored macules which vary from 4-5 mm in diameter to large confluent areas. Scales may be readily obtained by scraping the area with the fingernail. Lesions may appear on the trunk, upper arms, neck, and face.

**B. Laboratory Findings** Large, blunt hyphae and thick-walled budding spores may be seen under the low power objective when skin scales have been cleared in 10% potassium hydroxide. *M. furfur* cannot be cultured.

### Treatment and Prognosis.

Encourage good skin hygiene. Tinea versicolor responds readily to sodium thiosulfate, 10% aqueous solution, b.i.d.; or mild Whitfield's ointment, 1/4-1/2 strength (R 33, p. 86).

Lewis, G. M., & others: An Introduction to Medical Mycology. Year Book, 1958

## CUTANEOUS CANDIDIASIS (MONILIASIS)

### Essentials of Diagnosis

- Severe pruritus of vulva, anus, or body folds.
- Superficial, denuded, beefy red areas with or without satellite vesicopustules.
- Whitish curd-like concretions on the surface
- Fungus on microscopic examination of scales or curd.

Differentiate from intertrigo, seborrheic dermatitis, and tinea cruris involving the same areas

### General Considerations.

Cutaneous candidiasis is a superficial fungal infection which may involve almost any cutaneous or mucous surface of the body. It is particularly likely to occur in diabetics, during pregnancy, and in obese persons who perspire freely. Antibiotics may be contributory. Hypoparathyroidism may be complicated by candidiasis.

### Clinical Findings.

**A. Symptoms and Signs** Itching may be intense. Burning sensations are sometimes reported, particularly around the vulva and anus. The lesions consist of superficially denuded, beefy red areas in the depths of the body folds such as in the groin and the intergluteal cleft, beneath the breasts, at the angles of the mouth, and in the umbilicus. The peripheries of these denuded lesions are superficially undermined, and there may be satellite vesicopustules. Whitish, curd-like concretions may be present on the surface of the lesions (particularly in the oral and vaginal mucous membranes). Paronychia and interdigital erosions may occur.

**B. Laboratory Findings** Clusters of budding cells and short hyphae can be seen under the high power lens when skin scales or curd-like lesions have been cleared in 10% potassium hydroxide. The organism may be isolated on Sabouraud's medium.

### Complications

Candidiasis may spread from the skin or mucous membranes to the bladder, lungs, and other internal organs.

### Treatment.

**A. General Measures** Treat associated diabetes, obesity, or hyperhidrosis. Keep the parts dry and exposed to air as much as

possible. If possible, discontinue systemic antibiotics, if not, give nystatin (Mycostatin®) by mouth concomitantly in a dose of 1.5 million units t i d

#### B Local Measures

1 Nails and skin - Apply nystatin (Mycostatin®) cream, 100 000 units/Gm, or amphotericin B (Fungizone®) lotion 3-4 times daily. Gentian violet 1% or carbolfuchsin paint (Castellani's paint) may be applied 1-2 times weekly as an alternative.

2 Vulva, anal mucous membranes - Insert 1 nystatin (Mycostatin®) vaginal tablet (100 000 units) nightly for 2 weeks, or apply nystatin dusting powder (100 000 units/Gm) once or twice daily onto moist mucous membrane areas. Amphotericin B, gentian violet, or carbolfuchsin (see above) can also be used.

#### Prognosis

Cutaneous candidiasis may be intractable and prolonged particularly in children in whom the disturbance may take the form of a granuloma which resists all attempts at treatment.

Malbach, H I., & A M Kligman. The biology of experimental human cutaneous moniliasis (*Candida albicans*). Arch Dermat 85 113-37, 1962.

## PARASITIC INFESTATIONS OF THE SKIN

### SCABIES

#### Essentials of Diagnosis

- Nocturnal itching
- Pruritic vesicles and pustules in "runs" or "galleries," especially on the sides of the fingers and the heels of the palms
- Mites, ova, and black clots of feces visible microscopically

Distinguish from the various forms of pediculosis and from other causes of pruritus.

#### General Considerations

Scabies is a common dermatitis caused by infestation with *Sarcoptes scabiei*. An entire family may be affected. The infesta-

tion is generalized but usually spares the head and neck (although even these areas may be involved in infants). The mite is barely visible with the naked eye as a white dot. Scabies is usually acquired by sleeping or other close contact with an infested individual. This infestation is less common in the United States now than formerly.

#### Clinical Findings

A Symptoms and Signs. Itching occurs almost exclusively at night. The lesions consist of more or less generalized excoriations with small pruritic vesicles, pustules, and "runs" or "galleries" on the sides of the fingers and the heels of the palms. The run or gallery appears as a short irregular mark (perhaps 2-3 mm long), as if made by a sharp pencil. Characteristic lesions may occur on the nipples in females and as pruritic papules on the scrotum in males. Pruritic papules may be seen over the buttocks. Pyoderma is often the presenting sign.

B Laboratory Findings. The adult female mite may be demonstrated by probing the fresh end of a run or gallery with a pointed scalpel. The mite tends to cling to the tip of the blade. One may shave off the entire run or gallery (or, in the scrotum, a papule) and demonstrate the female mite, her ova, and small black dots of feces. The diagnosis should be confirmed by microscopic demonstration of the organism, ova, or feces.

#### Treatment & Prognosis

Unless the lesions are complicated by severe secondary pyoderma (see p. 53), treatment consists primarily of disinfection. If secondary pyoderma is present, potassium permanganate soaks (1:10,000) 1/2 hour 2-3 times daily may be indicated before definitive treatment is given.

Disinfection with gamma benzene hexachloride (Gammexane®, Kwell®), 0.5% in cream base, applied each night for 3 nights, is the treatment of choice. This preparation can be used before secondary infection is controlled. Alternative very effective drugs are Topicle® (benzyl benzoate) lotion or Eurax® (N-eroto-nolulldide) cream or lotion, either of which may be applied in the same way as gamma benzene hydrochloride.

Unless treatment is aimed at all infected persons in a family group, reinfestation will probably occur.

Lerner, M R., & A B Lerner. Dermatologic Medications, 2nd ed. Year Book, 1960.



## PEDICULOSIS

### Essentials of Diagnosis

- Pruritus with excoriation
- Nits on hair shafts, lice on skin or clothes
- Occasionally sky-blue macules (maculae caeruleae) on the inner thighs or lower abdomen in pubic louse infestation

Distinguish head louse infestation from seborrheic dermatitis, body louse infestation from scabies and pubic louse infestation from anogenital pruritus and eczema

### General Considerations

Pediculosis is a parasitic infestation of the skin of the scalp, trunk, or pubic areas. It usually occurs among people who live in overcrowded dwellings with inadequate hygiene facilities, although pubic lice may be acquired by anyone who sits on an infested toilet seat. There are 3 different varieties: (1) *Pediculosis pubis* is caused by *Phthirus pubis* (pubic louse, "crabs"); (2) *pediculosis corporis*, by *Pediculus humanus var. corporis* (body louse); (3) *pediculosis capitis* by *P. humanus var. capitis* (head louse).

Head and body lice are similar in appearance, 3-4 mm long. Head louse infestations may be transmitted by shared use of hats or combs. The body louse can seldom be found on the body, as the insect comes on the skin only to feed and must be looked for in the seams of the underclothing.

Trench fever, relapsing fever, and typhus may be transmitted by the body louse.

### Clinical Findings

Itching may be very intense in body louse infestations, and scratching may result in deep excoriations over the affected area. The clinical appearance is of gross excoriation. Pyoderma may be present and may be the presenting sign in any of these infestations. Head lice can be found on the scalp or may be manifested as small nits resembling pussy-willow buds on the scalp hairs close to the skin. They are easiest to see above the ears and at the nape of the neck. Body lice may deposit visible nits on the lanugo hair of the body. Pubic louse infestations are occasionally generalized, particularly in a hairy individual, the lice may even be found on the eyelashes and in the scalp.

### Treatment

Ten per cent chlorophenothane (DDT) in talcum or pyrophyllite, is extremely effective in all forms of pediculosis. Dust onto affected areas b i d for 2-3 days.

### Prognosis

Pediculosis responds promptly to topical treatment.

Goldman, L. Parasitic infestations of the skin. *P Clin North America* 3 625-37, 1956

## SKIN LESIONS DUE TO OTHER ARTHROPODS

### Essentials of Diagnosis

- Localized rash with pruritus
- Furuncle like lesions containing live arthropods
- Tender erythematous patches which migrate ("larva migrans")
- Generalized urticaria or erythema multiforme

Arthropods should be considered in the differential diagnosis of skin lesions showing any of the above symptoms.

### General Considerations

Some arthropods (e.g., most pest mosquitoes and biting flies) are readily detected as they bite. Many others are not, e.g., because they are too small, there is no immediate reaction, or they bite during sleep. Reactions may be delayed for many hours; many severe reactions are allergic. Patients are most apt to consult a physician when the lesions are multiple and pruritus is intense. Severe attacks may be accompanied by insomnia, restlessness, fever, and faintness or even collapse. Rashes may sometimes cover the body.

Many persons will react severely only to their earliest contacts with an arthropod, thus presenting pruritic lesions when traveling, moving into new quarters, etc. Body lice, fleas, bedbugs, and local mosquitoes should be borne in mind. Spiders are often incorrectly believed to be the source of bites; they rarely attack man, although the brown spider may cause severe necrotic reactions and the black widow spider (*Latrodectus mactans*) may cause severe systemic symptoms and even death.

In addition to arthropod bites, the most common lesions are venomous stings (wasps, hornets, bees, ants, scorpions) or bites (centipedes), dermatitis due to urticating hairs of caterpillars, dermatitis due to vesicating agents, furuncle-like lesions due to fly maggots or sandfleas in the skin and a linear creeping eruption due to a migrating larva.

### Clinical Findings

The diagnosis may be difficult when the patient has not noticed the initial attack but suffers a delayed reaction. Individual bites are frequently in clusters and tend to occur either on exposed parts (e.g., midges and gnats) or under clothing especially around the waist or at flexures (e.g., small mites or insects in bedding or clothing). The reaction is often delayed for 1-24 hours or more. Pruritus is almost always present, and may be all but intolerable once the patient starts to scratch. Secondary infection, sometimes with serious consequences, may follow scratching. Allergic manifestations, including urticarial wheals, are common. Papules may become vesicular. The diagnosis is greatly aided by searching for possible exposure to arthropods and by considering the occupation and recent activities of the patient. The principal arthropods are as follows:

- (1) Bedbugs - In crevices of beds or furniture, bites tend to occur in lines or clusters.
- (2) Fleas - In beds and floors. Rat fleas may attack the legs. Stick-tight fleas from poultry in the southern United States may be found actually attached to the skin. Tunga or chigoe fleas in South America and Africa burrow into the skin and swell, and secondary infection occurs readily following maltreatment.
- (3) Ticks - Usually picked up by brushing against low vegetation. Larval ticks may attack in large numbers and cause much distress, in Africa and India they have been confused with chiggers. Ascending paralysis may occasionally be traced to a tick bite, and removal of the embedded tick is essential.
- (4) Chiggers or red-bugs are larvae of trombiculid mites. A few species confined to particular countries and usually to restricted and locally recognized habitats (e.g., berry patches, woodland edge, lawns, brush, turkey mounds in Australia, poultry farms) attack man, often around the waist, on the ankles, or in flexures, raising intensely itching erythematous papules after a delay of many hours. The red chiggers may sometimes be seen in the center of papules which have not yet been scratched. Chiggers are the commonest cause of distressing multiple lesions (trombidiasis) due to arthropods.

(5) Bird mites - Larger than chiggers, infesting chicken houses, pigeon lofts, or nests of birds in eaves. Bites are multiple anywhere on the body, although poultry handlers are most often attacked on the hands and forearms. Room air conditioning units may suck in bird mites and infest the inhabitants of the room.

Rodent mites from mice or rats may cause similar effects. In the case of bird mites and rodent mites the diagnosis may readily be overlooked and the patient treated for other dermatoses or for psychogenic dermatosis. Intractable "acarophobia" may result from early neglect or misdiagnosis.

(6) Mites in stored products - These are white and almost invisible, and infest products such as copra ("copra itch"), vanilla pods ("vanillism"), sugar, straw, cotton seeds, and cereals. Persons who handle these products may be attacked, especially on the hands and forearms and sometimes on the feet. Infested bedding may occasionally lead to generalized dermatitis.

(7) Caterpillars of moths with urticating hairs. The hairs are blown from cocoons or carried by emergent moths, causing severe and often seasonally recurrent outbreaks after mass emergence, e.g., in some southern states of the U.S.A.

### Prevention

Arthropod infestations are best prevented by avoidance of contaminated areas, personal cleanliness, and disinfection of clothing, bed clothes, and furniture as indicated. Lice, chiggers, red-bugs, and mites can be killed by DDT applied to the head and clothing (it is not necessary to remove clothing). Benzyl benzoate and dimethylphthalate are excellent acaricides, clothing should be impregnated by spray or by dipping in a soapy emulsion.

### Treatment

Caution: Avoid local overtreatment.

Living arthropods should be removed carefully with tweezers after application of alcohol. Heat (lighted cigarette held near the skin) may make ticks and leeches detach themselves. Preserve in spirit for identification. (Caution: In endemic Rocky Mountain spotted fever areas, do not remove ticks with the bare fingers for fear of becoming infected.) Children in particular should be prevented from scratching.

Apply corticosteroid lotions or creams. If they are not available, croctamiton (Eurax<sup>®</sup>) cream or lotion may be used, it is a miticide as well as an antipruritic. Calamine lotion or a cool wet dressing is always appropriate. Antibiotic creams, lotions, or powders may be applied if secondary infection is suspected.

Avoid exercise and excessive warmth.

Codeine may be given for pain. Creams containing local anesthetics are not very effective and may be sensitizing. If an anesthetic cream is desired, lidocaine should be used since it is the least sensitizing.

See also Myiasis, p. 713.

## TUMORS OF THE SKIN

### General Considerations.

Areas exposed to chronic irritation (sun, chemicals, friction) are especially susceptible to neoplastic disease. The blue-eyed, sandy-complexioned person living under conditions of excessive sun exposure is a most likely candidate for skin cancer, especially of the squamous cell or basal cell variety. In the Southwestern United States skin cancer is the commonest skin problem, being even more common than acne vulgaris.

### Classification.

The following classification is admittedly oversimplified; almost any tumor arising from embryonal cells in the various stages of their development can be found in the skin

#### A. Malignant

1. Squamous cell carcinoma and senile keratoses usually occur on exposed parts in blue-eyed, sandy-complexioned persons. Squamous cell carcinoma may develop very rapidly, attaining a diameter of 1 cm. within 2 weeks. It appears as a small red, conical, hard nodule which quickly ulcerates. Metastasis may occur early. Keratoacanthomas are benign growths which resemble squamous cell carcinomas.

2. Basal cell carcinomas also occur mostly on exposed parts. They grow slowly, attaining a size of 1-2 cm. in diameter only after a year's growth. They present a waxy appearance, with telangiectatic vessels easily visible. Metastases either never occur or are caused by a squamous cell component of the tumor.

3. Paget's disease, considered by some to be a manifestation of apocrine sweat gland carcinomas, may occur around the nipple, resembling chronic eczema, or may involve apocrine areas such as the genitals.

B. Pre-malignant: Keratoses and leukoplakia have a marked tendency to be malignant. Actinic keratoses occur on exposed parts of the body in persons of fair complexion, and non-actinic keratoses may be provoked by exposure

to arsenic systemically or occupational irritants such as tars. In keratoses the cells are atypical and similar to those seen in squamous cell epitheliomas, but these changes are well contained by an intact epidermal-dermal junction. Leukoplakia is the counterpart of keratoses occurring on mucous membranes. One sees similar changes microscopically, plus the development of granular and horny layers which are not seen normally in mucous membranes or transitional epithelium. Leukoplakia may occur on the basis of individual predisposition or may be provoked by exposure to irritants such as excessive sunlight (lower lip), associated disease (e.g., syphilitic glossitis), excessive pipe smoking, and chewing tobacco.

#### C. Benign

1. Seborrheic warts, considered by some to be nevus, consist of benign overgrowths of epithelium which have a pigmented velvety or warty surface. They are extremely common, both on exposed and covered parts, and are commonly mistaken for melanomas or other types of cutaneous neoplasms.

2. Bowen's disease (intraepidermal squamous cell epithelioma) is relatively uncommon and resembles a plaque of psoriasis. The course is relatively benign, but 50% are associated with internal malignant tumors of various sorts.

#### D. Nevus

1. Cellular nevi are almost always benign, and almost everyone has at least a few of these lesions. They usually appear in childhood, and tend to spontaneous fibrosis during the declining years.

2. Junctional nevi, which consist of clear nevus cells and usually some melanin, have nevus cells on both sides of the epidermal junction. They are possible forerunners of malignant melanoma. If a nevus is on the palm, sole, or genitalia, or is subjected to continuous irritation, the possibility of melanomatous degeneration should be considered.

3. Compound nevi, composed of junctional elements as well as clear nevus cells in the dermis, may also tend to develop into malignant melanoma. Dermal cellular nevi are quite benign.

4. Blue nevi are benign, although they have been said to give rise occasionally to malignant melanoma. They are small, slightly elevated, and blue-black.

5. Epithelial nevi include several types of verrucous epithelial overgrowths, usually in linear distribution. Microscopically, cells found normally in the epidermis are present,

Such lesions rarely degenerate into squamous or basal cell carcinomas.

6 Freckles consist of excess amounts of melanin in the melanocytes in the basal layer of the epidermis. Ephelides or juvenile freckles, may be evanescent lentigines, or senile freckles, are usually larger and more persistent.

### Clinical Findings

A Symptoms and Signs The very absence of symptoms such as itching should lead one to suspect skin neoplasm when a growth is present. Soreness or pain (from ulceration or rapid growth) are occasionally reported.

Tumors of the skin consist of small nodules of varying rates of growth. The more rapid the growth, the more urgent the diagnosis. Any change in the texture or appearance of the skin should at least make the physician think of premalignant or malignant change. Whitish patches on mucous membranes, especially if their surfaces are rough, may suggest leukoplakia. Ulceration, crusting, or bleeding of any swollen area may point to cutaneous malignancy.

B Laboratory Findings Microscopic examination of biopsied or excised tissue usually is diagnostic for any of the lesions listed above. When malignant melanoma is suspected, the biopsy incision should include the entire lesion and a wide margin of normal skin.

### Complications

Squamous cell carcinoma is particularly likely to metastasize to regional lymph glands and then to distant sites. Basal cell carcinomas, if neglected, may cause extensive local destruction or occult spread may occur. Death may eventually take place with these "locally malignant" tumors as a result of invasion of vital structures. Melanomas spread similarly to the way in which squamous cell carcinomas do, and frequently spread hematogenously also.

### Treatment

A Surgical Measures Both benign and malignant tumors of the skin may be removed surgically by any of the following techniques:

- 1 Electrosurgery - Curettage with a dermal curet followed by electrodesiccation, removal with a cutting current, or electrocoagulation.
- 2 Scalpel surgery.
- 3 Chemosurgery (Mohs technique) - In this microscopically controlled technique the tissues are fixed with zinc chloride, dissected

bloodlessly, and then examined histologically. Tissue sites in which malignant cells persist are re-treated until tumor-free. This method should be considered only when other methods of treatment have failed.

### B Radiation (By a specialist)

1 X-ray therapy is successful for squamous cell and basal cell carcinomas. In general, malignant melanomas are unresponsive.

2 Radium and its products used interstitially or in contact may give excellent results.

### Prognosis

Cancer of the skin accounts for about 2% of all cancer fatalities in the United States. With the exception of melanomas, in which the outlook is grave, all cases are potentially curable if treated early. However, even with the best care, a 100% cure rate has never been attained.

Premalignant lesions such as senile arsenical and occupational keratoses and leukoplakia have a favorable prognosis if treated early. Arsenical keratoses and leukoplakia sometimes progress to squamous cell carcinoma and death despite the best of care.

Only one in 10-11 million cellular nevi develops into a malignant melanoma.

- Beerman, H. Tumors of the skin. Parts I and II. A review of recent literature. *Am J Med Sci* 211:480-504 and 212:470-505, 1945.
- Beerman, H. Some aspects of cutaneous malignancy. *Am J Med Sci* 233:456-72, 1957.

## MISCELLANEOUS SKIN DISORDERS

### PIGMENTARY DISORDERS

Melanin is formed in the melanocytes in the basal layer of the epidermis. Its precursor, the amino acid tyrosine, is slowly converted to dihydroxyphenylalanine (DOPA) by tyrosinase, and there are many further chemical steps to the ultimate formation of melanin. This system may be affected by external influences such as exposure to sun, heat, trauma, ionizing radiation, heavy metals, and changes in oxygen potential. These influences may result in hyperpigmentation, hypo-

pigmentation or both. Local trauma may destroy melanocytes temporarily or permanently, causing hypopigmentation, sometimes with surrounding hyperpigmentation as in eczema and dermatitis. Internal influences include melanocyte-stimulating hormone (MSH) from the pituitary gland, which is increased in pregnancy and in states in which there is an inadequate normal output of hydrocortisone by the adrenal cortex.

Other pigmentary disorders include those resulting from exposure to exogenous pigments such as carotenemia, argyria, deposition of other metals, and tattooing. Other endogenous pigmentary disorders are attributable to metabolic substances, including hemosiderin (iron) in purpuric processes, mercaptans, homogentisic acid (ochronosis), bile pigments, and carotenes.

### Classification

Pigmentary disorders may be classified as primary or secondary and as hyperpigmentary or hypopigmentary.

**A Primary Pigmentary Disorders** These are nevus or congenital and include pigmented nevus, Mongolian spots, incontinentia pigmenti, vitiligo, and albinism. Vitiligo is a genetically determined lack of pigmentation in which inhibited melanocytes are present in involved areas. Albinism, partial or total, occurs as a genetically determined recessive trait.

**B Secondary Pigmentary Disorders** Hyper- or hypopigmentation may occur following overexposure to sunlight or heat or as a result of excoriation or direct physical injury. Hyperpigmentation occurs in arsenical melanosis or in association with Addison's disease (due to lack of the inhibitory influence of hydrocortisone on the production of MSH by the pituitary gland). Several disorders of clinical importance are as follows:

1 **Chloasma (melasma)** This is essentially a nevus disorder occurring as patterned hyperpigmentation of the face. It is often associated with exaggeration of normal pigmentation elsewhere, such as in the axillae, the linea alba, the groins, and around the nipples. It is common during pregnancy as a result of the stimulus of MSH and tends to fade following each pregnancy.

2 **Berlucio hyperpigmentation** can be provoked by hypersensitivity to essential oils in perfumes, and these should be excluded wherever possible.

3 **Leukoderma** or secondary depigmentation may complicate atopic dermatitis, lichen planus, psoriasis, alopecia areata, lichen

simplex chronicus, and such systemic conditions as myxedema, thyrotoxicosis, syphilis, and toxemias. It may follow local skin trauma of various sorts, or may complicate dermatitis due to exposure to gold or arsenic. Antioxidants in rubber goods, such as monobenzyl ether of hydroquinone, can cause leukoderma from the wearing of gauntlet gloves, rubber pads in brassieres, etc. This is most likely to occur in Negroes.

4 **Ephelides** (juvenile freckles) and **lentigines** (senile freckles)

### Differential Diagnosis

One must distinguish true lack of pigment from pseudoachromia such as occurs in tinea versicolor, pityriasis simplex, and seborrheic dermatitis. It may be difficult to differentiate true vitiligo from leukoderma and even from partial albinism.

### Complications

The development of solar keratoses and epitheliomas is more likely to occur in persons with vitiligo and albinism. Vitiligo tends to create pruritus in anogenital folds. There may be severe emotional trauma in extensive vitiligo and other types of hypo and hyperpigmentations, particularly in naturally dark skinned persons.

### Treatment & Prognosis

There is no return of pigment in partial or total albinism; return of pigment is rare in vitiligo. In leukoderma repigmentation may occur spontaneously. The only effective treatment for vitiligo (with some response in 10-15% of patients only) is topical and oral therapy with methoxsalen (Meloxine<sup>®</sup>, Oxasoralen<sup>®</sup>). The topical preparation should be used in no greater strength than 1:10,000 concentration, as it may cause severe phototoxic effects and blisters. Methoxsalen is given systemically in a dosage of 20 mg each morning for weeks or months, and in combination with judicious exposure to sunlight may bring about repigmentation in vitiligo.

Localized ephelides and lentigines may be destroyed by careful application of a saturated solution of liquid phenol on a tightly wound cotton applicator. Chloasma and other forms of hyperpigmentation may be treated by protecting the skin from the sun and with cosmetics such as Covermark<sup>®</sup> (Lydia O'Leary Company) or A-Fli<sup>®</sup> (Texas Pharmacal Company). Cosmetics containing perfumes should not be used.

Bleaching preparations are of 2 principal types: 5% ammoniated mercury in a cream base, and monobenzyl ether of hydroquinone in liquid or cream form (Benoquin<sup>®</sup>). Benoquin<sup>®</sup>

is not without hazard, and it is best to start with a more dilute preparation than that offered by the manufacturer. The use of any bleach may result in unexpected hypo- or hyperpigmentation, particularly with prolonged use.

Treatment of other pigmentary disorders should be directed toward avoidance of the causative agent if possible (as in carotenemia) or treatment of the underlying disorder.

Symposium Psoriasis and radiant energy  
J Invest Dermat 32 132 391, 1959

### BALDNESS (Alopecia)

#### Baldness Due to Scarring

Cicatricial baldness may occur following chemical or physical trauma, severe bacterial or fungal infections, severe herpes zoster, chronic discoid lupus erythematosus, scleroderma, and excessive ionizing radiation. The specific cause is often suggested by the history, the distribution of hair loss, and the appearance of the skin, as in lupus erythematosus and other infections, and from burns or trauma. Biopsy may be necessary to differentiate lupus from the others.

Scarring alopecias are irreversible and permanent. There is no treatment.

#### Baldness Not Due to Scarring

Noncicatricial baldness may be classified according to distribution as alopecia universalis (generalized but not total hair loss), alopecia totalis (complete hair loss), and alopecia areata (patchy baldness).

Nonscarring alopecia may occur in association with various systemic diseases such as disseminated lupus erythematosus, cachexia, lymphomas, uncontrolled diabetes, severe thyroid or pituitary hypofunction, and dermatomyositis. The only treatment necessary is prompt and adequate control of the underlying disorder, in which case hair loss may be reversible.

Male pattern baldness, the most common form of alopecia, is of genetic predetermination. The earliest changes occur at the anterior portions of the calvarium on either side of the "widow's peak." Associated seborrhea is common, and is evident as excessive oiliness and erythema of the scalp, with scaling. Premature loss of hair in a young adult male may give rise to a severe neurotic reaction. The extent of hair loss is variable and unpre-

dictable. There is no treatment, and the patient should be cautioned not to spend money on advertised lotions or massage devices. Seborrhea may be treated as described on p 66.

**Diffuse idiopathic alopecia of women** is increasing in incidence. The cause is not known. The disease may not be apparent until about 80% of the hair is lost, and is then manifest as a diffuse thinning of the hair over the entire scalp (especially over the calvarium). The disease may be cyclic and recurrent over a period of many years, with little progression between episodes. These women may develop a neurotic reaction comparable in severity to cancerophobia. There is no treatment, although associated seborrhea should be controlled. It may be of psychologic benefit to prescribe topical medications if only in order to keep the patient from wasting money on valueless treatments. Triiodothyronine ( $T_3$ ) 5-25 mcg daily orally has been recommended.

**Alopecia areata** is of unknown cause and no pathologic scalp changes have been identified. The bare patches may be perfectly smooth or a few hairs may remain. Severe forms may be treated by injection of triamcinolone acetonide suspension into the patches, or by judicious use of systemic corticosteroid therapy, although systemic therapy is rarely justified unless the disease is of serious emotional or economic significance.

Systemic corticosteroids have also been used in the treatment of generalized and total alopecia. Alopecia areata is usually self-limiting, with complete regrowth of hair, but some mild cases are permanent, and the extensive forms are usually permanent, as are the totalis and universalis types also.

In trichotillomania (the pulling out of one's own hair) the patches of hair loss are irregular and growing hairs are always present, since they cannot be pulled out until they are long enough.

Behrman H T. The Scalp in Health and Disease. Mosby, 1952.

### HIRSUTISM

Hirsutism may be diffuse or localized, acquired or congenital. Essential hirsutism of women is most clearly manifested in the bearded area and on the upper lip, but it may be present on the chest and around the nipples as well. Endocrinologic studies may be nec-

essary to rule out excessive androgen secretion. Treatment is almost never of any value. If hirsutism is due to excessive androgen excretion, extirpation of the offending gland may be followed by disappearance of excessive hair.

Montagna, W., & R.A. Ellis: *The Biology of Hair Growth*. Academic, 1958.

## KELOIDS & HYPERTROPHIC SCARS

Keloids are tumors consisting of actively growing fibrous tissue which occur as a result of trauma or irritation in predisposed persons, especially those of Negro ancestry. The trauma may be relatively trivial, such as an acne lesion. Keloids behave as neoplasms, although they are not malignant. Spontaneous digitations may project from the central growth, and the tumors may become large and disfiguring. There may be itching and burning sensations with both types of tumor.

Hypertrophic scars, usually seen following surgery or accidental trauma, tend to be raised, red, and indurated. After a few months or longer they lose their redness and become soft and flat. Removal should not be attempted until all induration has subsided.

Intralesional injection of a corticoid suspension is effective against hypertrophic scars. The treatment of keloids is less satisfactory; surgical excision, x-ray therapy, and freezing with solid CO<sub>2</sub> or liquid nitrogen are used, as well as injection of corticoid suspensions into the lesions.

Asboe-Hansen, G.: Hypertrophic scars and keloids: etiology, pathogenesis, and dermatologic therapy. *Dermatologica* 120:178-84, 1960.

## NAIL DISORDERS

Nail changes are never pathognomonic of a specific systemic or cutaneous disease. All of the nail manifestations of systemic disorders may be seen also in the absence of any systemic illness.

Nail dystrophies cannot usually be related to changes in thyroid function, hypovitaminosis, nutritional disturbances, or generalized allergic reactions.

## Classification.

Nail disorders may be classified as (1) local, (2) congenital or genetic, and (3) those associated with systemic or generalized skin diseases.

### A. Local Nail Disorders:

1. Onycholysis (distal separation of the nails, usually of the fingers) is caused by excess exposure to water, soaps, detergents, alkalis, and industrial keratolytic agents.
2. Distortion of the nail occurs as a result of chronic inflammation of the nail matrix underlying the eponychial fold.
3. Discoloration and pithy changes, accompanied by a musty odor, are seen in ringworm infection.
4. Grooving and other changes may be caused by warts, nevi, and other growths impinging on the nail matrix.
5. Allergic reactions (to formaldehyde and resins in undercoats and polishes) involving the nail bed or matrix formerly caused hemorrhagic streaking of the nails, accumulation of keratin under the free margins of the nails, and great tenderness of the nail beds.
6. Beau's lines (transverse furrows) may be due to faulty manicuring.

### B. Congenital and Genetic Nail Disorders:

1. A longitudinal single nail groove may occur as a result of a genetic or traumatic defect in the nail matrix underlying the eponychial fold.
2. Nail atrophy may be congenital.
3. Hippocratic nails (club fingers) may be congenital.

### C. Nail Changes Associated With Systemic or Generalized Skin Diseases:

1. Beau's lines (transverse furrows) may follow any serious systemic illness.
2. Atrophy of the nails may be related to trauma or vascular or neurologic disease.
3. Hippocratic nails (club fingers) are occasionally related to prolonged anoxemia brought about by cardiopulmonary disorders.
4. Spoon nails are often seen in patients with anemia.
5. Stippling of the nails is seen in psoriasis.

## Differential Diagnosis.

It is important to distinguish congenital and genetic disorders from those caused by trauma and environmental disorders. Nail changes due to ringworm or dermatophyte fungi may be difficult to differentiate from onychia due to candida infections. Direct microscopic

examination of a specimen cleared with 10% potassium hydroxide or culture on Sabouraud's medium may be diagnostic. Ringworm of the nails may be closely similar to the changes seen in psoriasis and lichen planus. In which case careful observation of more characteristic lesions elsewhere on the body is essential to the diagnosis of the nail disorders.

#### Complications

Secondary bacterial infection occasionally occurs in onychodystrophies and leads to considerable pain and disability and possibly more serious consequences if circulation or innervation is impaired. Toenail changes may lead to ingrown nail in turn often complicated by bacterial infection and occasionally by exuberant granulation tissue. Poor manicuring and poorly fitting shoes may contribute to this complication. Cellulitis may result.

#### Treatment & Prognosis

Treatment consists usually of careful debridement and manicuring. Antifungal measures may be used in the case of onychomycosis and candidal onychia. Antibacterial measures may be used for bacterial complications. When nail changes are associated with specific diseases such as psoriasis and lichen planus one may use appropriate measures but the nail changes are usually very slow to reverse themselves. Congenital or genetic nail disorders are usually uncorrectable. Longitudinal grooving due to temporary lesions of the matrix such as warts, synovial cysts and other impingements may be cured by removal of the offending lesion.

Lamb J H. Nail disorders. In: *Dermatoses Due to Environmental and Physical Factors*. R B Rees (editor). Thomas, 1967.

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Pillsbury D M, Shelley W B & A M Kilgman. *Dermatology*. Saunders, 1956.

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## Simple Solutions: For Soaks &amp; Wet Dressings

Indications: For acute, red, swollen, itching, infected, weeping, or vesicular lesions.

Technic: Solutions must be applied cool (hot for infections).

(1) Basin soaks (2-5 quarts of solution) for hands and feet,  $\frac{1}{4}$  hour b.i.d.

(2) Wet dressings (for localized lesions). Use turkish towel, keep saturated with solution.

(a) Open dressings - for very acute lesions and when marked cleansing and soothing action is desired. Frequent applications are necessary (e. g.,  $\frac{1}{2}$  hour b.i.d.-q.i.d.).

(b) Covered dressings should not be used.

Agent	Action*	Range of Concentrations Used	Most Common Strength Used	Preparation of Solution of Most Commonly Employed Strength
Plain tap water	*	-	-	-
R 1 Sodium chloride	*	6 1000-15 1000 (0.6-1.5%)	0.9%	Two tsp. to 1 L. water.
R 2 Sodium bicarbonate	Antipruritic	1 50-1 20 (2-5%)	3%	Eight tsp. to 1 L. water.
R 3 Magnesium sulfate	Antipruritic	1 50-1 25 (2-4%)	3%	Eight tsp. to 1 L. water.
R 4 Aluminum subacetate sol.	Astringent	1 200-1 10 (0.5-10%)	5%	4 Domeboro® tablets or 50 ml. ( $\frac{1}{2}$ oz.) Burow's sol. to 1 L. water.
R 5 Silver nitrate	Astringent, antiseptic	1 10,000-1 200 (0.01-0.5%)	1 400 0.25%	10 ml. of 25% AgNO <sub>3</sub> solution or 2.5 Gm. (38 gr.) AgNO <sub>3</sub> to 1 L. water.
R 6 Mercury bichloride, small poison tablets	Astringent, antiseptic		1 10,000 (0.01%)	One tablet to 1 L. water. Poison. Do not use on denuded areas.
R 7 Potassium permanganate	Antipruritic, oxidizing, antiseptic, astringent	1 10,000-1 400 (0.01-0.25%)	1 10,000 0.01%	One 0.3 Gm. (5 gr.) tablet to 3 L. water or 0.1 Gm. ( $\frac{1}{2}$ gr.) tablet to 1 L. water.

\*All of the solutions listed have a drying, soothing, and cleansing action also.

## Powders

Name	Prescription	Instructions and Remarks
R 8 Absorbable gelatin sponge (non-sterile)	Gelfoam® powder, 10 Gm.	For leg ulcers and other indolent ulcers. It is absorbable hemostatic gelatin. Apply b.i.d. Use antibiotic topical powder also.
R 9 Talc		Simple dusting powder.
R 10 Antibiotic powder, topical	Oxytetracycline (Terramycin®), polymyxin-bacitracin (Neosporin®), or tetracycline (Achromycin®) topical powder.	For pyodermas. Dust on lesions b.i.d.
R 11 Nystatin (Mycostatin®)	R Nystatin, 100,000 U./Gm. dusting powder, 15 Gm.	Dusting powder b.i.d. for candidiasis.
R 12 Chlorophenothane (DDT)	R DDT 10.0 ( $\frac{1}{2}$ dr.) Talcum 100.0 ( $\frac{3}{4}$ oz.) q.s.ad	Apply 15-30 Gm. over the entire surface of underwear and treat seams on inside of shirt and trousers. Effective against all pediculoses.

## Lotions &amp; Emulsions

Liquid mixtures containing medicaments in solution or suspension are useful in a wide variety of localized and generalized skin lesions because they are easy to apply and remove. They have a marked drying effect and must not be used if this effect is undesirable. The following are some useful well known lotions.

Lotion and Action	Prescription	Instructions and Remarks
R 13 Calamine lotion (soothing drying)	Prepared calamine 80 (2 dr) Zinc oxide 80 (2 dr) Glycerin 20 (1/2 dr) Magma of bentonite 250 (8 dr) Lime water q s ad 1000 (3 1/3 oz)	Apply locally t i d q i d or p r n Use for acute dermatitis Avoid excessive drying by prolonged use of this lotion (as with other nonoily lotions) Add 1% phenol for antipruritic effect
R 14 Starch lotion (antipruritic soothing drying)	Starch corn 240 (6 dr) Zinc oxide 240 (6 dr) Glycerin 120 (3 dr) Lime water q s ad 1200 (4 oz)	Apply locally b i d and p r n Use for acute dermatitis Useful basic lotion to which other agents may be added
R 15 Oily lotion (soothing drying lubricating)	Zinc oxide 100 (2 1/2 dr) Olive oil Lime water ss q s ad 1200 (4 oz)	Apply locally t i d q i d or p r n Use for acute dermatitis Less drying than R 13 and 14
R 16 Coal tar lotion (soothing drying keratoplastic)	Sol coal tar 120 (3 dr) Zinc oxide 240 (6 dr) Starch 240 (6 dr) Glycerin 360 (9 dr) Water q s ad 1200 (4 oz)	Apply locally at night Scrub in a m Use for subacute dermatitis Useful mild stimulating lotion
R 17 Sun screen lotion (protective)	Para aminobenzoic acid 30 (1 dr) Emulsion base q s ad 300 (1 oz)	Apply locally to skin before each exposure to the sun
R 18 Acne lotion	Sulfur ppt Zinc sulfate ss 36 (1 dr) Sodium borate Zinc oxide ss 60 (1 1/2 dr) Acetone 300 (1 oz) Camphor water Rose water ss q s ad 1200 (4 oz)	Apply locally at night for acne
R 19 Sulfur-resorcinol lotion (drying antipruritic fungicidal keratolytic)	Sulfur ppt 40 (1 dr) Resorcinol 20 (1/2 dr) Zinc oxide 250 (6 dr) Talc 250 (6 dr) Ben onite 50 (1 dr) Alcohol 50% q s ad 1200 (4 oz)	Apply locally at night Scrub in a m For subacute and chronic dermatitis The sulfur and resorcinol concentrations may be doubled or tripled if more stimulating effect is desired
R 20 Tar scalp lotion (keratoplastic)	Sol coal tar 200 (5 dr) Castor oil 80 (2 dr) Alcohol 85% q s ad 1200 (4 oz)	Rub small quantity into scalp at night All purpose scalp lotion
R 21 Mercury salicylic hair lotion (keratoplastic)	Mercury bichloride 01 (1 1/2 gr) Salicylic acid 30 (45 gr) Alcohol 50% q s ad 1200 (4 oz)	Rub small quantity into scalp at night All purpose scalp lotion
R 22 Underarm lotion (antiperspirant)	Aluminum chloride 600 (2 oz) Glycerin 300 (1 oz) Distilled water q s ad 2400 (8 oz)	Apply small quantity to underarms each morning Useful antiperspirant.

## Ointment Bases

## Indications:

## Contraindications:

1. To correct fat deficiency in a dry skin.
2. To provide mechanical protection to the underlying lesions.
3. To help absorb or imbibe transudates from underlying lesions. (This holds true only for the hydrophilic preparations.)
4. To apply active medicinal agents to the skin.

1. Acute, inflamed, oozing lesions.
2. Hairy areas (except the hydrophilic preparations).

Preparation	Prescription	Properties
OINTMENTS		
R 23 Petrolatum, white		Chemically inert. Retards penetration of incorporated medicaments in some cases.
R 24 Petrolatum, hydrophilic	3% cholesterol in petrolatum, white wax, and stearyl alcohol.	Favors penetration of incorporated medicaments. Imbibes water (hydrophilic).
R 25 Wool fat, hydrous (lanolin)		Adheres well to skin, stable, favors penetration. Watch for sensitization.
R 26 Wool fat (anhydrous lanolin)		Imbibes water. Favors penetration. Watch for sensitization.
R 27 Zinc oxide ointment	20% zinc oxide in liquid petrolatum, wool fat, wax, and white petrolatum.	Mechanical protection, imbibes water, stiffens ointment (gives "body" to ointment) and makes it adhere to skin.
R 28 Theobroma oil (cocoa butter)		Melts at body temperature.

## CREAMS

(Contain water, more softening and soothing than ointments.)

R 29 Hydrophilic ointment	R Methylparaben	0.025 ( $\frac{3}{8}$ gr.)	Favors penetration, imbibes water, good vehicle for water-soluble medicaments.
	Propylparaben	0.015 ( $\frac{1}{4}$ gr.)	
	Stearyl alcohol	25.0 (6 dr.)	
	White petrolatum	25.0 (6 dr.)	
	Propylene glycol	12.0 (3 dr.)	
	Polyoxyl 40 stearate	5.0 (1 dr.)	
	Purified water, q.s. ad	100.0 ( $3\frac{1}{3}$ oz.)	
R 30 Rose-water ointment	R Spermaceti	12.5 (3 dr.)	"Cold cream" (water in oil), cooling and soothing effect.
	White wax	12.0 (3 dr.)	
	Expressed almond oil	56.0 (14 dr.)	
	Sodium borate	0.5 ( $7\frac{1}{2}$ gr.)	
	Rose water	5.0 (1 dr.)	
	Distilled water	14.0 ( $3\frac{1}{2}$ dr.)	
	Rose oil	0.02 ( $\frac{1}{3}$ min.)	
R 31 Emulsion base	R Duponol® C	1.6 (25 gr.)	Nonheating and nonirritating. Less messy than other creams and ointments.
	Cetyl alcohol	7.0 ( $1\frac{3}{4}$ dr.)	
	Stearyl alcohol	7.0 ( $1\frac{3}{4}$ dr.)	
	White petrolatum	20.0 (5 dr.)	
	Heavy liquid petrolatum	2.0 ( $\frac{1}{2}$ dr.)	
	Butoben®	0.05 ( $\frac{3}{4}$ gr.)	
	Distilled water, q.s. ad	100.0 ( $3\frac{1}{3}$ oz.)	

## PASTES

(High powder content. Promote evaporation and cooling, decrease vesiculation.)

R 32 Zinc oxide paste (Lassar's paste)	R Zinc oxide	25.0 (6 dr.)	Mechanical protective. Increases adhesion but decreases penetration of medicaments.*
	Starch	25.0 (6 dr.)	
	Petrolatum, white,		
	q.s. ad	100.0 ( $3\frac{1}{3}$ oz.)	

\*Add 2% cholesterol or 5% acetyl alcohol to increase water-imbibing power.

## Ointments, Miscellaneous Standard Prescriptions

Common Name	Prescriptions	Instructions and Remarks
R 33 Ointment of benzoic and salicylic acid (Whitfield's)	P Benzoic acid 60 (1 1/2 dr) Salicylic acid 30 (3/4 dr) Polyethylene glycol ointment q s ad 100.0 (3 1/3 oz)	Apply locally at bedtime Fungicide Often prescribed in 1/2 1/4 strength Not for acute or subacute lesions
R 34 Aluminum acetate ointment (1 2 3)	R Aluminum acetate solution 10.0 (2 1/2 dr) Wool fat 20.0 (5 dr) Zinc oxide paste 30.0 (1 oz)	Apply locally to skin p r n Valuable on receding inflammatory processes
R 35 Sulfur salicylic acid ointment	R Sulfur 10.0 (2 1/2 dr) Salicylic acid 10.0 (2 1/2 dr) Petrolatum q s ad 100.0 (3 1/3 oz)	Apply locally p r n Potent fungicide Note Not for acute or subacute lesions
R 36 Calamine cream	P Hydrophilic ointment U S P 33.0 (8 dr) Calamine lotion 66.0 (16 dr)	Apply locally p r n Good general purpose cream Vehicle for water soluble agents
R 37 Ammoniated mercury ointment	R Ammoniated mercury 5.0 (75 gr) Liquid petrolatum 3.0 (3/4 dr) Petrolatum q s ad 100.0 (3 1/3 oz)	Apply locally to skin p r n For seborrheic dermatitis and psoriasis
R 38 Kaolin and sulfur ointment	R Kaolin 10.0 (2 1/2 dr) Sulfur ppt 10.0 (2 1/2 dr) Zinc oxide ointment q s ad 100.0 (3 1/3 oz)	Apply locally at bedtime A good substitute exfoliating paste for acne
R 39 Gamma benzene hexachloride	R Kwell <sup>®</sup> ointment 60.0 (2 oz)	Apply as directed Useful scabicide
R 40 Hydrocortisone ointment or cream	Available as 0.25 1.5 1 and 2.5% ointment in 5 Gm to 120 Gm quantities	Apply a thin film b i d Combined with tar antibiotics or tetracycline hydroxyquin Do not use in dendritic keratitis

## Solutions Tinctures &amp; Paints

R 41 Gentian violet	1% aqueous solution	Antiseptic (gram-positive organisms) and fungicide (Candida)
R 42 Sodium thiosulfate	10% aqueous solution	Fungicide (especially for <i>trich versicolor</i> )
R 43 Silver nitrate	1 10% aqueous solution	Cauterizing and astringent for fissures and ulcers
R 44 Chrysarobin	4% in chloroform	For cardinal paronychia
R 45 Nitromersol	0.5% (1:200 tincture) (Metaphen <sup>®</sup> )	Bacteriostatic and germicidal
R 46 Alcoholic Whitfield's solution	R Salicylic acid 2.0 (1/2 dr) Benzoic acid 4.0 (1 dr) Alcohol 40% q s ad 120.0 (4 oz)	Apply locally Effective fungicidal combination May substitute bay rum for alcohol
R 47 Benzoin compound tincture	Full strength	Useful for sbraded fissured or ulcerated areas
R 48 Soft soap liniment	65% soap	Useful detergent
R 49 Antiseborrheic shampoo	Seisun <sup>®</sup> Foxtex <sup>®</sup> Sebulex <sup>®</sup> Capseb <sup>®</sup> Alvinine <sup>®</sup> Iloquin <sup>®</sup> Sebical <sup>®</sup>	Contain detergents salicylic acid sulfur compounds tar or quinoline Some may cause excess oiliness and hair loss
R 50 Triethanolamine emulsion	R Triethanolamine 4.0 (1 dr) Oleic acid 8.0 (2 dr) Mineral oil q s ad 100.0 (3 1/3 oz)	Add up to 5 parts of water to make a shampoo

# 5...

## Eye

Daniel Vaughan

### NONSPECIFIC MANIFESTATIONS

#### Pain.

The 2 most serious eye disorders which cause pain are iritis and acute glaucoma. If neither is present, look for a corneal abrasion or foreign body, or a foreign body concealed beneath the upper eyelid.

#### Blurred Vision.

The most important causes of blurred vision without pain are cataract, central retinal vein thrombosis, vitreous hemorrhage, central retinal artery occlusion and macular degeneration. Almost all of these occur in the older age groups.

#### Conjunctival Discharge.

Discharge is usually caused by bacterial conjunctivitis.

#### "Eyestrain."

This is a common ocular complaint which usually means eye discomfort associated with prolonged reading or close work. Significant refractive error or phoria (usually exophoria with poor convergence) should be ruled out.

#### Photophobia.

Photophobia suggests iritis, keratitis, or corneal ulcer.

#### "Spots."

"Spots before the eyes" are vitreous opacities which usually have no clinical significance, in unusual instances they signify impending retinal detachment or posterior uveitis

#### Headache.

Headache is only occasionally due to ocular disorders. The 2 most common ocular causes of headache are uncorrected refractive error and muscular imbalance especially exophoria.

Differential Diagnosis of Common Causes of Inflamed Eye

	Acute Conjunctivitis	Acute Iritis	Acute Glaucoma	Corneal Trauma or Infection
Incidence	Extremely common	Common	Uncommon	Common
Discharge	Moderate to copious	None	None	Watery or purulent (or both)
Vision	Normal	Slightly blurred	Markedly blurred	Usually blurred
Pain	None	Moderate	Severe	May be pain or irritation
Conjunctival redness	Diffuse	Mainly cir- cumcorneal	Diffuse	Diffuse
Cornea	Clear	Usually clear	Steamy	May be corneal abrasion, foreign body, or ulcer due to virus, bacte- rium, or fungus
Pupil size	Normal	Small	Large	Normal
Pupillary light re- sponse	Normal	Poor	Poor	Normal
Intraocular pressure	Normal	Normal	Elevated	Normal
Smear	Causative organisms	No organ- isms	No organ- isms	No organisms unless taken direct- ly from cornea (bacteria, fungi)

**Diplopia.**

Double vision is most commonly due to paralysis of an extraocular muscle (usually a lateral rectus) caused by inflammation or other disorders of the sixth nerve

**OCULAR EMERGENCIES****ACUTE (ANGLE-CLOSURE)  
GLAUCOMA**

Acute glaucoma occurs only if the iris-corneal angle is narrow. If the pupil dilates spontaneously or is dilated with a mydriatic or cycloplegic the angle will close and an attack of acute glaucoma is precipitated for this reason it is a wise precaution to examine the iris-corneal angle before instilling these drugs. About 1% of the population have narrow iris-corneal angles but many of these never develop glaucoma.

Patients with acute glaucoma seek treatment immediately because of extreme pain and blurring of vision. The eye is red, the cornea is steamy and the pupil is dilated. Intraocular pressure is elevated (tonometer examination).

Acute glaucoma must be differentiated from acute iritis (in which the cornea is clear and the pupil small) and from conjunctivitis (in which there is no blurring, a clear cornea, and a pupil of normal size).

Peripheral iridectomy within 24-72 hours after onset of symptoms will usually result in permanent cure. Untreated acute glaucoma results in complete blindness within 3-5 days after onset of symptoms.

See references listed under Chronic (Open-angle) Glaucoma p. 105

**FOREIGN BODIES**

If a patient complains of "something in my eye" and gives a consistent history, he usually has a foreign body even though it may not be readily visible. Almost all foreign bodies, however, can be seen under oblique illumination with a hand flashlight.

Note the time, place, and other circumstances of the accident. Test visual acuity (if possible, before treatment is instituted) for legal as well as medical reasons as a basis for comparison in the event of complications.

**Conjunctival Foreign Body.**

Foreign body of the upper tarsal conjunctiva is suggested by pain and blepharospasm and by an apparently clear bulbar conjunctiva and cornea. After instilling a local anesthetic, evert the lid by grasping the lashes gently and exerting pressure on the midportion of the outer surface of the upper lid with an applicator. If a foreign body is present it can be easily removed by passing a sterile wet cotton applicator across the conjunctival surface.

**Corneal Foreign Body.**

When a corneal foreign body is suspected but is not apparent on simple inspection, stain the cornea with sterile fluorescein and examine with an ocular loupe if possible. The foreign body may then be removed with a sterile wet cotton applicator. An antibiotic should be instilled, e.g. polymyxin-bacitracin (Polysporin<sup>®</sup>) ointment. It is not necessary to patch the eye but the patient must be examined in 24 hours for secondary infection of the crater.

Early infection is manifested by a white necrotic area around the crater and a small amount of gray exudate. These patients should be referred immediately to an ophthalmologist.

In the absence of infection the corneal wound will heal by epithelial regeneration in 36-48 hours, otherwise weeks or months may be required. Untreated corneal infection may lead to severe corneal ulceration, panophthalmitis and loss of the eye.

**Intraocular Foreign Body.**

A patient with an intraocular foreign body should be referred immediately to an ophthalmologist. With delay the ocular media become progressively more cloudy, and a foreign body visible shortly after the injury may not be visible several hours later. The foreign body can often be removed through the point of entry with a magnet if this is attempted soon enough.

The visual prognosis is poor in most cases.

**CORNEAL ABRASIONS**

A patient with a corneal abrasion complains of severe pain, especially with movement of the lid over the cornea.

Record the history and visual acuity. Examine the cornea and conjunctiva with a light and loupe to rule out foreign body. If an abrasion is suspected but cannot be seen, instill sterile fluorescein into the conjunctival sac; the area of corneal abrasion will stain a deeper green than the surrounding cornea.

Instill polymyxin-bacitracin (Polysporin®) ophthalmic ointment and apply a bandage with firm pressure to prevent movement of the lid. The patient should be observed on the following day to be certain that the cornea has healed without infection. If there is no infection, a layer of corneal epithelial cells will line the crater within 24 hours. It should be emphasized that the intact corneal epithelium forms an effective barrier to infection. If the corneal epithelium is broken, the cornea is extremely susceptible to infection.

Thomas, C. I. Cornea and sclera. Annual review. Arch. Ophth. 65:243-318, 1961

### CONTUSIONS

Contusion injuries of the eye and surrounding structures may cause ecchymosis ("black eye"), subconjunctival hemorrhage, edema or rupture of the cornea, hemorrhage into the anterior chamber (hyphema), rupture of the root of the iris (iridodiolysis), traumatic paralysis of the pupillary muscle (mydriasis), paralysis or spasm of the muscles of accommodation, traumatic cataract, subluxation or luxation of the lens, vitreous hemorrhage, retinal hemorrhage and retinal edema (most common in the macular area), detachment of the retina, rupture of the choroid (posteriorly), fracture of the orbital floor ("blowout fracture"), and optic nerve injury. Many of these injuries may not be apparent for days or weeks. Patients with moderate to severe contusions should be seen by an ophthalmologist.

Any injury severe enough to cause intraocular hemorrhage, particularly anterior chamber hemorrhage (hyphema) involves the danger of secondary hemorrhage which may cause intractable glaucoma and permanent damage to the eye. Any patient with traumatic hyphema should be put at absolute bed rest for 6-7 days with both eyes bandaged. Secondary hemorrhage rarely occurs after this time.

### ULTRAVIOLET KERATITIS (Actinic Keratitis)

Ultraviolet burns of the cornea are usually caused by exposure to a welding arc. There are no immediate symptoms, but about 12 hours later the patient complains of agonizing pain, severe photophobia, and blepharospasm. Examination with sterile fluorescein and the slit lamp shows diffuse punctate staining of both corneas.

Treatment consists of local steroid therapy, systemic analgesics, and sedatives as indicated. All patients recover within 24 hours without complications.

See reference under Corneal Abrasions, above.

### CORNEAL ULCER

Corneal ulcers constitute a medical emergency. The typical gray, necrotic corneal ulcer is preceded by a corneal foreign body or abrasion. The eye is red with lacrimation and conjunctival discharge, and the patient complains of blurred vision, pain, and photophobia.

Prompt treatment, instituted often within hours after onset of symptoms, is essential to prevent complications. Otherwise permanent visual impairment, ranging from blurring to total blindness, may result.

Corneal ulcer must be differentiated from iritis (small pupil and clear cornea) and conjunctivitis (no blurring of vision, clear cornea, copious discharge).

#### Pneumococcal ("Acute Serpiginous") Ulcer.

*Diplococcus pneumoniae* is the commonest bacterial cause of corneal ulcer. The early ulcer is gray and fairly well circumscribed, and has a marked tendency to spread centrally.

Since the pneumococcus is sensitive to both sulfonamides and antibiotics, local therapy is usually effective. If untreated, the cornea may perforate and the eye may be lost. Concurrent dacryocystitis, if present, should also be treated.

#### *Pseudomonas* Ulcer.

A less common but much more virulent cause of corneal ulcer is *Pseudomonas aeruginosa*. The ulceration characteristically starts in a small area, usually in the center, and spreads rapidly, frequently causing perforation of the cornea and loss of the eye within 48 hours. It often follows minor corneal injury when *pseudomonas*-contaminated fluorescein solution has been instilled into the eye. *Pseudomonas aeruginosa* usually produces a pathognomonic bluish-green pigment.

Early diagnosis and vigorous treatment with polymyxin locally plus streptomycin and a sulfonamide systemically are essential if the eye is to be saved.

#### Herpes Simplex (Dendritic) Keratitis.

Corneal ulceration caused by herpes simplex virus is probably more common than all bacterial ulcers combined. It is almost always unilateral, and may affect any age group of either sex. It is often preceded by upper

respiratory tract infection with fever and cold sores

The commonest finding is of one or more dendritic ulcers (superficial branching gray areas) on the corneal surface. These are composed of clear vesicles in the corneal epithelium when the vesicles rupture the areas assume green with fluorescein. Although the dendritic figure is its most characteristic manifestation, herpes simplex keratitis may appear in a number of other configurations.

Treatment consists of removing the virus containing corneal epithelium without disturbing Bowman's membrane or the corneal stroma. This is best done by an ophthalmologist. Do not give local or systemic steroids as they enhance the activity of the virus by impairing the natural inflammatory response and so may lead to perforation of the cornea and loss of the eye.

IDU (5-iodo deoxyuridine) a drug originally developed as an antineoplastic agent has been reported by Kaufman to be effective against herpes simplex keratitis. It is applied locally as 0.1% solution, 2 drops in the affected eye every hour day and night for about 3 days. If improvement is noted after that time give the drug every 2 hours for 2 days and then gradually withdraw over a period of 3 more days. Extensive clinical trials are now in progress and if the encouraging results reported by Dr. Kaufman and his co-workers can be reproduced with some consistency in clinical practice an important contribution to the treatment of a potentially blinding eye disease will have been made. It is hoped also that IDU may be the first of many chemotherapeutic and viral drugs.

Kaufman H E Nesburn A B & E D

Maloney Treatment of herpes simplex keratitis Arch Ophthalmol 67:583-91 1962

[Write reference for IDU (IDUR) therapy]

Thomas C I See reference on p 99

Thygeson P & S J Kimura Differential diagnosis of superficial forms of keratitis and keratoconjunctivitis Tr Pac Coast Ophth Soc 37:153-71 1957

Vaughan D G Jr Corneal ulcers Survay Ophthalmol 3:703-15 1958

## CHEMICAL CONJUNCTIVITIS & KERATITIS

Chemical burns are treated by irrigation the eyes with saline solution or plain water as soon as possible after exposure. Do not neutralize an acid with an alkali or vice versa as the heat generated by the reaction may cause

further damage. Alkali injuries require irrigation for at least one half hour since alkalis are not precipitated by the proteins of the eye as are acids. If possible proparacaine (Ophthaine® Ophthelc®) 0.5% should be instilled locally before irrigation in order to relieve the pain. The pupil should be dilated with 5% homatropine. Hydrocortisone ointment 1.5% is placed in each eye 2-6 times daily. Complications include symblepharon, corneal scarring and secondary infection.

## GONOCOCCIC CONJUNCTIVITIS

Gonococcal conjunctivitis which may cause corneal ulceration is manifested by a copious purulent discharge. The diagnosis may be confirmed by a stained smear of the discharge. Prompt treatment with local and systemic penicillin is required.

## SYMPATHETIC OPHTHALMIA (Sympathetic Uveitis)

Sympathetic ophthalmia is a rare severe bilateral granulomatous uveitis. The etiology is not known but the disease may occur anywhere from 2 weeks to several years after a penetrating injury near the ciliary body. The injured (exciting) eye becomes inflamed first and the fellow (sympathizing) eye second. Symptoms and signs include blurred vision with light sensitivity and redness.

The best treatment of sympathetic ophthalmia is prevention. Any severely injured eye (e.g. one with perforation of the sclera and ciliary body with loss of vitreous) should be enucleated within 2 weeks after the injury. Every effort should be made to secure the patient a reasoned consent to the operation. In established cases of sympathetic ophthalmia systemic steroid therapy may be helpful. Untreated the disease progresses gradually to bilateral blindness.

## LACERATIONS

### Lids

If the lid margin is lacerated the patient should be referred for specialized care since permanent notching may result. Other lid lacerations may be sutured just as any other skin laceration.



## Conjunctiva.

In superficial lacerations of the conjunctiva sutures are not necessary. In order to prevent infection, instill a broad-spectrum antibiotic ointment into the eye 2-3 times a day until the laceration is healed.

## Cornea or Sclera.

Keep examination and manipulation at an absolute minimum, since pressure may result in extrusion of the intraocular contents. Bandage the eye lightly and cover with a metal shield which rests on the orbital bones above and below. Instruct the patient not to squeeze his eyes shut and transport him on a stretcher to an ophthalmologist.

## ORBITAL CELLULITIS

Orbital cellulitis is manifested by an abrupt onset of fever and focal inflammation of the eye, and proptosis. It is usually caused by a pyogenic organism. Immediate treatment with systemic antibiotics is indicated to prevent brain abscess. The response to antibiotics is usually satisfactory.

Benedict, W. L.: Diseases of the orbit. *Am J. Ophth.* 33:1-10, 1950  
 Winter, C. F.: The orbit. Annual review  
*Arch. Ophth.* 66:405-29, 1961.

## VITREOUS HEMORRHAGE

Hemorrhage into the vitreous body may obscure retinal detachment. Treatment by an ophthalmologist is indicated.

Irvine, A. R., Jr.: The lens and vitreous  
 Annual review. *Arch. Ophth.* 65:592-609,  
 1961.

## COMMON OCULAR DISORDERS

### CONJUNCTIVITIS

Conjunctivitis is the commonest eye disease in the Western Hemisphere. It may be acute or chronic. Most cases are exogenous and due to bacterial or viral infection, though endogenous inflammation may occur (e.g.,

phlyctenular conjunctivitis, a sensitivity response to circulating tuberculo-protein). Other causes are allergy, chemical irritations, and fungal or parasitic infection. The mode of transmission of infectious conjunctivitis is usually direct contact, i.e., via fingers, towels, or handkerchiefs, to the opposite eye or to other persons.

Conjunctivitis must be differentiated from iritis, glaucoma, corneal trauma, and keratitis (see p. 97). Herpes simplex keratitis is unilateral, refractory to treatment, and is generally made worse by the use of steroids.

### Bacterial Conjunctivitis.

The organisms found most commonly in bacterial conjunctivitis are *Diplococcus pneumoniae* and *Staphylococcus aureus*. Both produce a copious, purulent discharge in both eyes. There is no pain or blurring of vision. The disease is usually self-limited, lasting about 10-14 days if untreated. A sulfonamide or antibiotic ointment instilled locally t.i.d. will usually clear the infection in 3-4 days.

### Viral Conjunctivitis.

One of the commonest causes of viral conjunctivitis is adenovirus type 3, which is usually associated with pharyngitis, fever, malaise, and preauricular adenopathy. Locally, the palpebral conjunctivae are red and there is a copious watery discharge and scanty exudate. Children are more often affected than adults, and contaminated swimming pools are frequently the source of the virus. There is no specific treatment, although local sulfonamide therapy may prevent secondary infection. The disease usually lasts about 10 days.

Trachoma is the commonest disease known to man with the exception of the common cold. It is caused by a large atypical virus similar to the viruses of psittacosis and lymphogranuloma venereum, and only occurs under conditions of poor hygiene and overcrowding. Trachoma is manifested by chronic bilateral conjunctival redness and mild itching, a watery discharge, and scanty exudate. The diagnosis is usually based at least in part on epidemiologic considerations. Sulfonamides are the drugs of choice, e.g., sulfisoxazole (Gantrisin®), 3 Gm. daily by mouth for one week and then 2 Gm. daily for 2 weeks, combined with Achromycin® in oil, 2 drops in each eye q.i.d. for 6 weeks. Without treatment, trachoma progresses to involve the cornea, causing corneal scarring which leads to blindness.

Inclusion blennorrhoea (swimming pool conjunctivitis) is an unusual disease manifested by bilateral conjunctival redness and a copious exudate. It responds well to local sulfonamide ointment therapy 4 times daily, local broad-spectrum antibiotics are equally effective.

With treatment, the disease can be cleared in one week; otherwise it may persist for 3 months to one year.

#### Allergic Conjunctivitis.

Allergic conjunctivitis is common. It causes bilateral tearing, itching, and redness, and a minimal stringy discharge. It is usually chronic and recurrent. Local steroid therapy is often effective.

#### Fungal & Parasitic Conjunctivitis.

Most fungal and parasitic conjunctivides are rare in most parts of the world, and are usually unilateral. They often present with a localized inflammatory granuloma in the conjunctiva. A more common example is Leptothrix conjunctivitis which occurs in persons in close contact with cats.

#### Ophthalmia Neonatorum.

Ophthalmia neonatorum is any infection of the conjunctiva in the newborn. Common types are chemical (silver nitrate), bacterial (staphylococci, pneumococci, gonococci), and viral (inclusion blennorrhoea).

Silver nitrate conjunctivitis occurs within 24 hours after birth, bacterial conjunctivitis within 2-5 days, and inclusion blennorrhoea within 5-10 days. The diagnosis is made by examination of a smear of conjunctival scrapings, although sometimes the material must be cultured.

Silver nitrate conjunctivitis will clear in a few days without treatment, or steroid ointment may be applied to hasten healing. Bacterial conjunctivitis and inclusion blennorrhoea respond well to specific antibiotic or sulfonamide therapy.

Bacterial conjunctivitis in newborn infants may be prevented by instilling silver nitrate solution, 1%, or penicillin ointment, 100,000 units/Gm., into the conjunctival sac of each eye immediately after birth. More concentrated silver nitrate solutions will cause permanent corneal scarring, and even 1% solution frequently causes chemical conjunctivitis, many ophthalmologists therefore recommend that penicillin be substituted. The disadvantage of penicillin prophylaxis is that it may favor the emergence of penicillin-resistant strains of staphylococci in the nursery. In some states of the U.S.A., silver nitrate prophylaxis is required by law.

Thygeson, P.: Diseases of the Conjunctiva. In Berens, The Eye and Its Diseases, Saunders, 1950.

Thygeson, P.: Published writings of Phillips Thygeson. Am. J. Ophth. (Thygeson Proc.) 34 5-6, 1951. (Part II of May issue.)

Thygeson, P.: Viral infections of the eye and adnexa. Survey Ophth. 3 568-83, 1958.

#### PINGUECULA

Pinguecula is a yellow nodule of hyaline and elastic tissue on either side of the cornea (more commonly on the nasal side) in the area of the lid fissure. The nodules rarely grow, but inflammation is common. No treatment is indicated. Pinguecula is common in persons over 35 years of age.

#### PTERYGIUM

Pterygium is a fleshy, bilateral, triangular encroachment of a pinguecula onto the nasal side of the cornea and is usually associated with constant exposure to wind and dust. Excision is indicated if the growth approaches the pupillary area.

#### UVEITIS

Uveitis is any inflammation of the uveal tract (iris, ciliary body, and choroid). Inflammation of the iris primarily is called anterior uveitis or iritis, inflammation of the choroid (and usually the retina as well) is called posterior uveitis or chorioretinitis.

Uveitis may be either granulomatous (exogenous) or nongranulomatous (endogenous), the latter is more common. The disease is usually unilateral, and signs and symptoms are similar in both types, varying only in intensity. Early diagnosis and treatment are important to prevent the formation of posterior synechias.

Uveitis must be differentiated from conjunctivitis (conjunctival discharge, normal size pupil, no blurring of vision), acute glaucoma (steamy cornea and dilated pupil); and corneal ulcer (localized or diffuse corneal opacification).

#### Nongranulomatous Uveitis (Endogenous).

Nongranulomatous uveitis (iritis) occurs in about 10% of all patients with rheumatoid arthritis. The iris and ciliary body are primarily affected, but occasional foci are found in the choroid. The process is usually acute (acute anterior uveitis), with exacerbations paralleling the rheumatic process.

The onset is acute, with marked pain, redness, photophobia, and blurred vision. A circumcorneal flush, caused by dilated limbal blood vessels, is present. Fine white keratic precipitates (KPs) on the posterior surface of the cornea can be seen with the slit lamp or with a loupe. The pupil is small, and there may be a collection of fibrin with cells in the

anterior chamber. If posterior synechias are present, the pupil will be irregular and the light reflex will be absent.

Local and systemic steroid therapy tends to shorten the course. Warm compresses will relieve pain. Atropine, 2%, 2 drops into the affected eye b.i.d., will prevent posterior synechia formation and alleviate photophobia. The prognosis is good. Recurrences are common.

#### Granulomatous Uveitis (Exogenous).

Granulomatous uveitis usually follows invasion by the causative organism, e.g., *Mycobacterium tuberculosis* or *Toxoplasma gondii*, although these pathogens are rarely recovered. Any or all parts of the uveal tract may be affected, but the infection is usually mild.

The onset is usually slow, and the affected eye may be only slightly and diffusely red. Vision is more blurred than would be expected in view of the apparent mildness of the process. Pain is minimal or absent and photophobia is slight. The pupil may be normal or, if posterior synechias are present, slightly smaller than normal and irregular. Large gray "mutton fat" keratic precipitates on the posterior surface of the cornea may be seen with the slit lamp or loupe. The anterior chamber may be cloudy. Iris nodules are commonly present, and there may be a vitreous haze. Fresh lesions of the choroid appear yellow when viewed with the ophthalmoscope.

Treatment is usually unsatisfactory since the causative agent is not known. The pupil should be kept dilated with atropine and associated systemic disease treated as indicated. The visual prognosis is at best only fair.

Coles, R.S.: Uveitis. A review. *Survey Ophthalm.* 5:355-404, 1960.

Kimura, S.J.: The uveal tract. *Annual review. Arch. Ophthalm.* 67:357-72, 1962.

Maumenee, A.E. (editor): Uveitis. Symposium by the Council for Research in Glaucoma and Allied Diseases. *Survey Ophthalm.* 4:217-423, 1959.

#### HORDEOLUM

Hordeolum is a common staphylococcal abscess which is characterized by a localized red, swollen, acutely tender area on the upper or lower lid. Internal hordeolum is a meibomian gland abscess which points to the skin or to the conjunctival side of the lid, external hordeolum or sty (infection of the glands of Moll or Zeis) is smaller and on the lid margin.

The primary symptom is pain, the intensity of which is directly related to the amount of swelling.

Treatment consists of warm compresses. Incision is indicated if resolution does not begin within 48 hours. An antibiotic or sulfonamide instilled into the conjunctival sac every 3 hours is beneficial during the acute stage. Without treatment, internal hordeolum may lead to cellulitis of the lid and orbit.

Theodore, F.H.: The lids, lacrimal apparatus, and conjunctiva. *Annual review. Arch. Ophthalm.* 67:56-87, 1962.

#### CHALAZION

Chalazion is a common granulomatous inflammation of a meibomian gland, characterized by a hard, nontender swelling on the upper or lower lid. It may be preceded by a sty. The majority point toward the conjunctival side.

If the chalazion is large enough, vision will be distorted. The conjunctiva of the everted lid is red and elevated.

Treatment consists of excision by an ophthalmologist.

See previous references.

#### TUMORS

Verrucae and papillomas of the skin of the lids can usually be excised by the general physician. Malignancy should be ruled out by microscopic examination of the excised material.

Reese, A.B.: Tumors of the Eye. Hoeber, 1951.

#### BLEPHARITIS (Granulated Eyelids)

Blepharitis is a common chronic, bilateral inflammation of the lid margins. It may be (1) ulcerative or staphylococcal (*Staphylococcus aureus*), or (2) nonulcerative or seborrheic. The latter type may be caused by *Pityrosporum ovale*, although the relationship is not definite. Both types are usually present. Seborrhea of the scalp, brows, and frequently of the ears is almost always associated with seborrheic blepharitis.

Symptoms are irritation, burning, and itching. The eyes are "red-rimmed," and

scales or "granulations" can be seen clinging to the lashes. In the staphylococcal type the scales are dry, the lids are red and ulcerated and the lashes tend to fall out. In the seborrheic type the scales are greasy, ulceration is absent and the lid margins are less red. In the more common mixed type both dry and greasy scales are present and the lid margins are red and may be ulcerated.

Cleanliness of the scalp, eyebrows and lid margins is essential to effective local therapy. Scales must be removed from the lids daily with a damp cotton applicator.

Staphylococcal blepharitis is treated with an antistaphylococcal antibiotic or sulfonamide eye ointment applied with a cotton applicator once daily to the lid margins. For seborrheic blepharitis nitrofurazone (Furacin) ointment is recommended once daily at bedtime on the lid margins.

See reference under Hordeolum above

## ENTROPION AND ECTROPION

Entropion (inward turning of the lid usually the lower) occurs occasionally in older people as a result of degeneration of the lid fascia. Surgery is indicated if the lashes rub on the cornea.

Ectropion (outward turning of the lower lid) is fairly common in elderly people. Surgery is indicated if ectropion causes excessive tearing, exposure keratitis or a cosmetic problem.

See reference under Hordeolum above

## DACRYOCYSTITIS

Dacryocystitis is a common infection of the lacrimal sac. It may be acute or chronic and occurs most often in infants and in persons over 40. It is usually unilateral and is always secondary to obstruction of the nasolacrimal duct.

### Adult Dacryocystitis

The cause of obstruction is usually unknown but a history of trauma to the nose may be obtained. In acute dacryocystitis the usual infectious agent is *Staphylococcus aureus* or *Streptococcus pyogenes*. In the chronic form, *Diplococcus pneumoniae* or occasionally, *Hemophilus influenzae* is found. Mixed infections do not occur.

Acute dacryocystitis is characterized by pain, swelling, tenderness and redness in the tear sac area. Purulent material may be expressed. In chronic dacryocystitis tearing and discharge are the principal signs. Mucoid material may be expressed from the tear sac.

Acute dacryocystitis responds well to antibiotic therapy but recurrences are common if the obstruction is not removed. The chronic form can be kept latent by using antibiotic eye drops but relief of the obstruction is the only cure.

### Infantile Dacryocystitis

Normally the nasolacrimal ducts open spontaneously during the first month of life. In a few cases one of the ducts fails to canalize and a secondary pneumococcal dacryocystitis develops. When this happens, forceful massage of the tear sac is indicated and antibiotic or sulfonamide drops should be instilled in the conjunctival sac 4-5 times daily. If this is not successful after 3 weeks, probing of the nasolacrimal duct is indicated regardless of the infant's age. To minimize infection penicillin is given 1 M. 2 days before probing and the tear sac is irrigated freely just before probing. One probing is effective in about 75% of cases. In the remainder cure can usually be achieved by repeated probing.

See reference under Hordeolum p. 103

## CHRONIC (OPEN-ANGLE) GLAUCOMA

### Essentials of Diagnosis

- Insidious onset in older age groups
- No symptoms in early stages
- Gradual loss of peripheral vision over a period of years
- Persistent elevation of intraocular pressure as determined by serial tonometric examinations
- Note "Halos" around lights are not present unless the intraocular tension is very high

Chronic glaucoma is not easily confused with other conditions.

### General Considerations

In chronic glaucoma the intraocular pressure is consistently elevated. Over a period of months or years this results in optic atrophy and loss of vision varying from a slight constriction of the peripheral visual fields to complete blindness. The cause of the decreased

rate of aqueous outflow in chronic glaucoma has not been clearly demonstrated. Although a definite familial tendency exists, no specific pattern has been demonstrated.

In the United States it is estimated that there are 2 million people with glaucoma, about half of these cases are undetected. About 90% of all cases of glaucoma are of the chronic open-angle type.

### Clinical Findings.

Patients with chronic glaucoma have no symptoms initially. There may be slight cupping of the optic disk. The visual fields gradually constrict, but central vision remains good until late in the disease.

Measurement of the intraocular pressure with a tonometer is the single most important diagnostic test in the detection of glaucoma. The normal intraocular pressure is about 10-25 mm. Hg. Except in acute glaucoma, however, the diagnosis is never made on the basis of one tonometric measurement, since various factors can influence the pressure (e.g., diurnal variation). Transient elevations of intraocular pressure do not constitute glaucoma (for the same reason that periodic elevations of BP do not constitute hypertensive disease).

### Prevention.

All persons over age 35 should have a tonometric examination every 3 years. This is as easily done by the general physician or internist as by the ophthalmologist. If there is a family history of glaucoma, annual examination is indicated. Mydriatic and cycloplegic drugs should be used with discretion.

### Treatment.

Most patients can be controlled with miotics, e.g., pilocarpine, 1-2%, 3-4 times daily. Pilocarpine apparently increases the rate of outflow of aqueous through Schlemm's canal. Acetazolamide (Diamox®) and other carbonic anhydrase inhibitors (see p. 237) are also useful in decreasing the rate of aqueous production. Epinephrine, 1%, also decreases aqueous production and has recently become more widely used in open-angle glaucoma. (Caution: Epinephrine is contraindicated if the iris-corneal angle is narrow.) Treatment must be continued throughout life.

### Prognosis.

Untreated chronic glaucoma which begins at age 40-45 will probably cause complete blindness by age 60-65. Early diagnosis and adequate control will preserve useful vision throughout life in most cases.

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Duke-Elder, W.S.: The diagnosis and treatment of simple glaucoma. *Survey Ophth.* 6: 117-20, 1961.

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## RETINAL DETACHMENT

### Essentials of Diagnosis

- Blurred vision in one eye becoming progressively worse. ("A curtain came down over one of my eyes")
- No pain or redness
- Visible detachment on ophthalmoscopic examination

Sudden partial loss of vision in one eye may also be due to vitreous hemorrhage or thrombosis of the central retinal vein or one of its branches.

### General Considerations.

Detachment of the retina is usually spontaneous but may be secondary to trauma. Spontaneous detachment occurs most frequently in persons over 50 years old. In both types predisposing causes such as aphakia, high myopia, peripheral cystic degeneration of the retina, and chorioretinitis are usually present. Detachment may occur in a healthy eye if the trauma is severe enough.

### Clinical Findings.

As soon as the retina is torn, a transudate from the choroidal vessels, mixed with vitreous, combines with the force of gravity to strip the retina from the choroid. The superior temporal area is the most common site of detachment. The area of detachment increases with time, causing corresponding progressive visual loss. Central vision remains intact until the macular portion of the retina becomes detached.

On ophthalmoscopic examination the retina is seen hanging in the vitreous like a gray cloud. The vitreous may be cloudy. A retinal tear, usually crescent-shaped and red or orange, may also be seen.

### Treatment.

All cases of retinal detachment should be referred immediately to an ophthalmologist. If it is necessary to transport him a long distance, his head should be immobilized so that the detached portion of the retina will fall back into its normal position. For example, a patient with a superior temporal retinal detachment in the right eye should lie only on his back or right side. Position is less important for a short trip.

Treatment consists of drainage of the sub-retinal fluid and closure of the retinal tears by diathermy or scleral buckling (or both). This produces an adhesive inflammatory reaction which binds the retina to the choroid. Photocoagulation is of value in a limited number of cases of minimal detachment. It consists of focussing a strong light ("burning glass") through the pupil to create an artificial inflammation between the choroid and the retina.

### Prognosis

About 80% of uncomplicated cases can be cured with one operation; an additional 10% will need repeated operations; the remainder never heal satisfactorily. The prognosis is worse if retinal detachment is total; if there are many vitreous strands; or if the detachment is of long duration. Without treatment, retinal detachment almost always becomes total in 6-12 months. Because the same predisposing causes are present, retinal detachment in the other eye occurs in about 30% of cases.

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- Plachet, D. K., & others. Symposium - retinal detachment. *Tr Am Acad Ophth* 62 189-225, 1958.

The degree of visual loss corresponds to the density of the cataract.

### Treatment

Only a small percentage of senile cataracts require surgical removal. Degree of visual impairment is the prime criterion; other factors are age, general health, and the patient's occupation. Treatment of senile cataract consists of removal of the lens followed by refractive correction with a spectacle cataract lens. Contact lenses are replacing the heavy cataract lenses in younger patients and those requiring surgery in one eye only.

### Prognosis

If surgery is indicated, lens extraction improves visual acuity in 95% of cases. The remainder either have preexisting retinal damage or develop postoperative complications such as glaucoma, retinal detachment, or infection.

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## CATARACT

### Essentials of Diagnosis

- Blurred vision, progressive over months or years.
- No pain or redness.
- Visible opacities in the lens on ophthalmoscopic examination.

### General Considerations

A cataract is a lens opacity. Cataracts are usually bilateral. They may be congenital or may occur as a result of trauma or, less commonly, systemic disease. Senile cataract is by far the most common type; almost all persons over 60 have some degree of lens opacity.

### Clinical Findings

Even in its early stages a cataract can be seen through a dilated pupil with an ophthalmoscope, a slit lamp, or an ordinary hand illuminator. As the cataract matures the retina will become increasingly difficult to visualize, until finally the fundus reflex is absent. At this point the pupil is white and the cataract is mature.

## STRABISMUS

### Essentials of Diagnosis

- History of eye turning.
- Demonstration of deviation by corneal reflection test and cover test.
- Reduced visual acuity in the deviating eye in established cases.

### General Considerations

About 5% of children are born with or develop a malfunction of ocular coordination known as strabismus. In descending order of frequency, the eyes may deviate inward (esotropia), outward (exotropia), upward (hyperopia) or downward (hypotropia). The cause is not known, but fusion is lacking in all cases. If a child is born with straight eyes but has inherited "weak fusion," he may develop strabismus.

### Clinical Findings

Children with frank strabismus first develop diplopia. They soon learn to suppress the image from the deviating eye and thus the vision in that eye fails to develop.

Most cases of strabismus are obvious, but if the angle of deviation is small or if the strabismus is intermittent, the diagnosis may be obscure. The best method for detecting strabismus is to direct a light toward each pupil from a distance of 1-2 feet. If the corneal reflection is seen in the center of each pupil, the eyes can be presumed to be straight at that moment.

As a further diagnostic test ("cover test"), cover the right eye with an opaque object and instruct the patient to fix his gaze on the examining light with the left eye. If fusion is weak, covering the right eye will disturb the fusion process sufficiently to allow the right eye to deviate, and this can be observed behind the cover. The right eye swings back into alignment when the cover is removed. In some instances the covered eye will maintain the deviated position after removing the cover. Ask the patient to follow the examining light with both eyes open to the right, left, up, and down to rule out extraocular muscle paralysis. If there is a history of deviation but it cannot be demonstrated, and if there are no other ocular disorders, the patient should be re-examined in 6 months.

#### Prevention.

Almost all cases of amblyopia due to strabismus can be prevented by routine visual acuity examination of all pre-school children.

#### Treatment.

The objectives in the treatment of strabismus are (1) good visual acuity in each eye, (2) straight eyes, for cosmetic purposes, and (3) coordinate function of both eyes.

The best time to initiate treatment is at the age of 6 months. If treatment is delayed beyond this time the child will favor the straight eye and suppress the image in the other eye, this results in failure of visual development (amblyopia ex anopsia) in the deviating eye.

If the child is under 7 years of age and has an amblyopic eye, the amblyopia can be cured by patching the good eye. At one year of age, patching may be successful within one week, at 6 years it may take a year to achieve the same results, i.e., to equalize the visual acuity in both eyes. Prolonged patching does not impair vision in the good eye.

There is no firm rule about the proper time for surgery, but the general dictum, "The earlier the better after age one," is a useful guide. If the visual acuity is the same in both eyes and the eyes can be made reasonably straight through surgery (or with glasses, as in the case of accommodative esotropia), eye exercises may assist the patient in learning to use his eyes together (fusion).

#### Prognosis.

The prognosis is more favorable for strabismus which has its onset at age 2-3 than for strabismus which is present at birth, better for divergent (outward deviation) than for convergent strabismus; and better for intermittent than for constant strabismus.

Allen, J. H.: *Strabismus Ophthalmic Symposium II*, 2nd ed. Mosby, 1958.

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\* \* \*

### PRINCIPLES OF TREATMENT OF OCULAR INFECTIONS

#### Identification of Pathogen.

Before one can determine the drug of choice, the causative organisms must be known. For example, a pneumococcal corneal ulcer will respond to treatment with a sulfonamide, penicillin, or any broad-spectrum antibiotic, but this is not true in the case of corneal ulcer due to *Pseudomonas aeruginosa*, which responds only to vigorous treatment with polymyxin or colistimethate (Coly-Mycin®). Another example is staphylococcal dacryocystitis, which, if it does not respond to penicillin, is most likely to respond to erythromycin (Ilotycin®), Erythrocin®, or novobiocin (Cathomycin®, Albamycin®).

#### Choice of Alternative Drugs.

In the treatment of infectious eye disease, e.g., conjunctivitis, one should always use the drug which is the most effective, the least likely to cause complications and, if possible, the least expensive. It is also preferable to use a drug which is not usually given systemically, e.g., sulfacetamide, polymyxin, or bacitracin. Of the available antibacterial agents, the sulfonamides come closest to meeting these specifications. Two reliable sulfonamides for ophthalmic use are sulfisoxazole (Gantrisin®) and sodium sulfacetamide (Sulamyd®). The sulfonamides have the added advantages of low allergenicity and effectiveness against certain viruses (e.g., trachoma virus). They are available in ointment or solution form.

Two of the most effective broad-spectrum antibiotics for ophthalmic use are chloramphenicol (Chloromycetin®) and neomycin. Both of these drugs have some effect against gram-negative as well as gram-positive organisms. Other antibiotics frequently used are erythromycin (Ilotycin®, Erythrocin®), the tetracyclines, bacitracin, and polymyxin (Aerosporin®).

Combined bacitracin polymyxin (Polysporin<sup>®</sup>) ointment is often used prophylactically for the protection it affords against both gram positive and gram negative organisms

#### Method of Administration

Most ocular anti-infective drugs are administered locally. Systemic administration is required for all intraocular infections, corneal ulcer, orbital cellulitis, dacryocystitis, and any severe external infection which does not respond to local treatment.

#### Ointments vs. Liquid Medications

Ointments have greater therapeutic effectiveness than solutions since contact can be maintained longer (for 30-60 minutes). However, they do cause blurring of vision if this must be avoided, solutions should be used.

### TECHNIQUES USED IN THE TREATMENT OF OCULAR DISORDERS

#### Liquid Medications

Place the patient in a chair with both eyes open and looking up. Retract the lower lid slightly and instill 2 drops of liquid into the lower cul-de-sac. Have the patient look down while finger contact on the lower lid is maintained. Do not let him squeeze his eye shut.

#### Ointments

Ointments are instilled in the same manner as liquids. While the patient is looking down, lift out the lower lid and drop the medication into the conjunctival sac.

#### Self-medication

The same techniques are used as described above, except that drops should be instilled with the patient lying down.

#### Eye Bandage

Most eye bandages should be applied firmly enough to hold the lid securely against the cornea. An ordinary patch consisting of gauze-covered cotton is usually sufficient. Tape is applied from the cheek to the forehead. If more pressure is desired, use 2 bandages. The black eye patch cannot be sterilized and therefore is seldom used in modern medical practice.

#### Warm Compresses

A clean towel or washcloth soaked in tap water slightly warmer than a hot tub bath is applied to the affected eye. Warm compresses are used 2-3 times a day for 10-15 minutes.

#### Removal of a Superficial Corneal Foreign Body

Record the patient's visual acuity if possible and instill a local anesthetic. With the patient sitting or lying down, an assistant should direct a strong light into the eye so that the rays strike the cornea obliquely. Using either a loupe or a slit lamp, the physician locates the foreign body on the corneal surface. He may remove it with a sterile wet cotton applicator or, if this fails, with a spud, holding the lids apart with the other hand to prevent blinking. An antibacterial ointment (e.g., Polysporin<sup>®</sup>) is instilled after the foreign body has been removed.

It is preferable not to patch the eye after removal of a foreign body, since most patients are more comfortable without one. It is essential, however, that the patient be seen on the following day to be certain that no infection is present and that healing is progressing.

### PRECAUTIONS IN THE MANAGEMENT OF OCULAR DISORDERS

#### Use of Local Anesthetics

Unsupervised self-administration of local anesthetics is dangerous because the patient may further injure an anesthetized eye without knowing it. Furthermore, most anesthetics, particularly butacaine (Butyn<sup>®</sup>), delay healing. Butacaine also elicits a high incidence of allergic responses. Note: Do not give patients any local anesthetics to take home.

#### Errors in Diagnosis

The most common error is treatment for conjunctivitis when the correct diagnosis is the more serious iritis (anterior uveitis), glaucoma, or corneal ulcer.

#### Pupillary Dilation

Cycloplegics and mydriatics should be used with caution. Dilating the pupil can precipitate an attack of glaucoma if the patient has a narrow iris-corneal angle.

The most common cycloplegics are atropine, scopolamine, and homatropine. Phenylephrine (Neo-Synephrine<sup>®</sup>) and hydroxyamphetamine hydrobromide (Paredrine<sup>®</sup>) are commonly used mydriatics.

#### Local Steroid Therapy

Local ophthalmic steroid preparations, e.g., hydrocortisone, have become increasingly popular during recent years because of their anti-inflammatory effect on the conjunctiva, cornea, and iris. However, repeated use of local steroids presents 2 serious hazards: herpes simplex (dendritic) keratitis and



fungal overgrowth. All of the steroids enhance the activity of the herpes simplex virus, apparently by decreasing the normal inflammatory response in the corneal tissue of the host. Perforation of the cornea occasionally occurs when the steroids are used during the more active stage of a herpes simplex corneal infection. In the treatment of any corneal inflammation, particularly if the corneal epithelium has been broken, the prolonged use of hydrocortisone is sometimes complicated by fungal infection (e.g., *Candida albicans*), and this may lead to loss of the eye.

Any patient on whom ophthalmic steroids are used should be observed carefully for complications. The steroids should not be used unless specifically indicated, e.g., in iritis.

#### Contaminated Eye Medications.

The intact sclera and corneal epithellum are an effective barrier to infection. However, once these tissues have been broken by a laceration or foreign body they are susceptible to bacterial infection. Ophthalmic solutions must therefore be handled with the same degree of care as fluids intended for I.V. administration.

Tetracaine (Pontocaine<sup>®</sup>), proparacaine (Ophthaine<sup>®</sup>, Ophthetic<sup>®</sup>), physostigmine and fluorescein are most likely to become contaminated. The most dangerous is fluorescein, as this solution is frequently contaminated with *Pseudomonas aeruginosa*, an organism which grows better in the cornea than in any known culture medium and which can destroy the eye within hours.

The following rules should be observed in handling eye medications: (1) Obtain solutions in small amounts from the pharmacy. (2) Be certain that the solution is sterile as prepared by the pharmacist and that it contains an effective antibacterial agent. (3) Date the bottle at the time it is procured. (4) Use glass-top or screw-top bottles and dispense the solution with individual sterile droppers. Individual sterile disposable eye dropper units (e.g., Minims<sup>™</sup>) should be used exclusively in the emergency room and operating room. (5) Fluorescein and tetracaine should be autoclaved at least once a week; repeated autoclaving does not cause deterioration of the drugs. Proparacaine should also be autoclaved once a week and should be discarded after 12 autoclavings. It is permissible to use solutions sold in plastic bottles if any unused portion is discarded within 1 week after it is opened.

#### Fungal Overgrowth.

Since the antibiotics, like the steroids, when used over a prolonged period of time in bacterial corneal ulcers, favor the development of secondary fungal infection of the cornea, the sulfonamides should be used whenever they are adequate for the purpose.

#### Sensitization

A significant portion of a soluble substance instilled in the eye may pass into the blood stream. This suggests that an antibiotic instilled into the eye can sensitize the patient to that drug and cause a hypersensitivity reaction upon subsequent systemic administration.

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## 6...

# Ear, Nose, & Throat

Wayne W Deutsch Sidney Levin & R Morton Monson

## DISEASES OF THE EAR

### HEARING LOSS

#### Classification

**A Nerve Deafness (Perceptive Sensori-neural)** Disturbance in the inner ear neural structures or nerve pathways leading to the brain stem

**B Conductive Deafness** Disturbance of the sound transmission mechanism of the external or middle ears prevents sound waves from reaching the inner ear

**C Mixed Type** Disturbance in both the conductive and nerve mechanisms

**D Functional Deafness** Hearing loss for which no organic lesion can be detected

#### General Considerations

Five to 10% of people have a hearing defect temporarily or permanently which is severe enough to impair their normal function. Hearing loss may occur at any age and produces disability depending upon the degree of loss, the age at which it occurs (interference with language and speech development) and whether one or both ears are affected.

Nerve type hearing loss may be congenital due to birth trauma, maternal rubella, erythroblastosis fetalis, or malformations of the inner ear, or it may be due to traumatic injury to the inner ear or eighth nerve, vascular disorders with hemorrhage or thrombosis in the inner ear, toxic agents (dihydrostreptomycin, streptomycin, kanamycin, quinine, aspirin), bacterial and viral infections (mumps, etc.), severe febrile illnesses, Meniere's disease, posterior fossa tumors, multiple sclerosis, and presbycusis.

Conductive hearing loss may also be congenital due to malformations of the external or middle ear. Trauma may produce perforation of the eardrum or disruption of the ossicu-

lar chain. Inflammatory middle ear disease may produce serous otitis media, acute or chronic purulent otitis media, or adhesive otitis media. Otosclerosis, a common familial conductive hearing loss with onset in middle life, produces ankylosis of the stapes by overgrowth of new spongy bone; the etiology is not known.

#### Clinical Findings

The older patient will usually be aware of hearing loss of significant degree, and an accurate history is of importance to determine etiology. All the causes of hearing loss listed above must be investigated. In particular, the age at onset, degree of loss, progression, associated tinnitus or vertigo, exposure to head trauma, sound trauma, ototoxic drugs, previous infection, and severe febrile illnesses must be checked.

In infants and young children the diagnosis is often suggested by failure of speech development, lack of cooperation, inability to concentrate, and slow progress in learning.

A complete ear, nose, and throat examination is essential in all patients with hearing loss. Most important is examination of the ear canal, eardrum, and middle ear with the magnifying otoscope to detect even slight abnormalities. Attention must be given to obstructing or infected adenoid and tonsils, nasal and sinus infection, and evidences of other cranial nerve disturbance.

Special tests of value are as follows:

(1) Spoken voice test

(2) Watch tick test

(3) Tuning fork tests. The 500 and 1000 cps forks are the most important. These tests detect lateralization of the sounds of the fork and demonstrate comparative disturbances of air conduction and bone conduction (to distinguish conductive loss and nerve type loss).

(4) Audiometric tests (pure tone, speech tests, and other highly specialized audiometric tests) give accurate quantitative estimates of the degree of hearing loss.

(5) Labyrinthine tests give valuable objective evidence of inner ear function. An absent or altered labyrinthine response is

quite significant. The test is done by irrigating the ear canals with hot or cold water to produce nystagmus and vertigo. The response in each ear should be equal.

## Treatment

### A Hearing Loss in Children

1 Nerve deafness - There is no medical or surgical treatment for nerve deafness. Management consists of rehabilitation and education. A hearing aid is valuable if there is residual hearing. Speech reading and speech training must be incorporated into the educational program.

2 Conductive deafness - Acute suppurative otitis media should be treated with early myringotomy in addition to medical management. Acute catarrhal otitis media may be treated medically, but the patient must be carefully followed to ensure that the infection completely resolves. Otherwise, residual fluid in the middle ear may produce a persistent conductive hearing loss due to "glue ear" or adhesive otitis media. Antibiotics in adequate doses and nasal decongestants should be administered for at least 7 days and often longer. This is necessary to prevent smoldering, partially eradicated infections that may recur in a few days with antibiotic-resistant organisms. Paracentesis and aspiration may be necessary.

Serous otitis media is common in children as well as in adults. Vigorous early treatment will usually reverse the hearing loss. Investigation and treatment of contributing nasal allergy or infection combined with aspiration of fluid from the middle ear is effective. Removal of obstructing or infected tonsils and adenoidal tissue is often necessary. In protracted and recurrent cases repeat adenoidectomy may be necessary. Follow-up eustachian tube inflations are often required. The progress of each case must be carefully followed by audiometric testing.

Chronic otitis media in childhood should be treated vigorously to attempt to cure the disease and preserve or restore hearing. Many cases respond to cleansing followed by instillation of powders (e.g., chloramphenicol and boric acid) or antibiotic solutions. Attention must again be directed to underlying nasal or sinus disease and infected or obstructing tonsils and adenoid. Other cases require surgery of the middle ear or mastoid (or both). Bilateral congenital anomalies of the external ear canal and middle ear can sometimes be corrected surgically. This should be done before plastic repair of the external ear is made. Small central perforations of the eardrum can be closed by patching with a Cargile membrane as an office procedure. Larger central per-

forations may be closed with a vein graft or skin graft. Marginal perforations usually require skin grafting and mastoid exploration.

### B Hearing Loss in Adults

1 Nerve deafness - Nerve loss due to acoustic trauma will sometimes improve over a period of 6 months if the patient can avoid exposure to loud noise. There is no medical or surgical treatment for other types of nerve deafness. A hearing aid should not be recommended for a patient with nerve deafness unless audiometric testing (pure tone and speech) indicates that the patient will probably learn to use the instrument satisfactorily. The learning of speech reading (lip reading) by a hard-of-hearing patient is of definite value in his rehabilitation.

2 Conductive deafness - Important advances have been made recently in the surgical treatment of middle ear deafness. Otosclerosis may be treated successfully by the fenestration operation or by a direct operation on the fixed stapes through the ear canal and middle ear. The most recent techniques involve removal of the stapes and replacement of the foot plate with a graft (vein fat or gelfoam) and replacement of the stapes crura with a prosthesis (wire or polyethylene tube).

Perforations of the eardrum can be repaired by vein or skin grafting (myringoplasty).

Mastoid and middle ear operations have been designed for the treatment of suppurative and the removal of cholesteatoma and to preserve or improve hearing by skin grafting and by replacing or realigning the ossicular chain (tympanoplasty).

Serous otitis media in adults is treated in the same manner as in children.

Nerve deafness due to Meniere's disease will sometimes respond to early adequate and prolonged treatment. A fluctuating loss has a more favorable prognosis than a sudden severe loss. The basis of medical management is sodium restriction (1 Gm sodium diet), antihistamines (e.g., diphenhydramine or dimenhydrinate q i d for 1-2 months), potassium substitution for sodium (KCl 1 Gm t i d for 1-2 weeks), vasodilators (nicotinic acid in flushing doses q i d), and reassurance.

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## DISEASES OF THE EXTERNAL EAR

### 1 IMPACTED CERUMEN

Cerumen is the normal secretion of the cartilaginous part of the ear canal which serves a protective function. Normally it dries and falls out of the ear canal but it may accumulate within the canal because of dryness or scaling of the skin, narrowing or tortuosity of the ear canal or excess hair in the ear canal. It may be packed in deeper by repeated unskilled attempts to remove it. There are usually no symptoms until the canal becomes completely occluded when a feeling of fullness, deafness or tinnitus or a cough due to reflex stimulation of the vagus nerve may occur. Otoscopy reveals the mass of yellow, brown or black wax which may be sticky and soft or waxy or stony hard.

If the mass is firm and movable it may be removed through the speculum with a dull ring curette or a cotton applicator. If this is painful the impaction may be removed by irrigation with water at body temperature directing the stream of water from a large syringe at the wall of the ear canal and catching the solution in a basin held beneath the ear. If the impaction is very hard and adherent and cannot be readily removed by irrigation it must be softened by repeated instillations of olive ear drops, glycerin or peroxide and irrigated again in 2-3 days.

### 2 EXTERNAL OTITIS

#### Differential Diagnosis

Diffuse eczematoid dermatitis of the ear canal, diffuse infected dermatitis and furunculosis of the ear canal must be distinguished from dermatitis due to contact with foreign objects (hearing aids, earphones) or infected material draining from the middle ear through a perforated eardrum.

External otitis may vary in severity from a diffuse mild eczematoid dermatitis to cellulitis or even furunculosis of the ear canal. It is frequently referred to as a fungal infection of the ear, although in many cases there is no infection and the reaction is a contact dermatitis (earphones, earrings) or a variant of seborrheic dermatitis. Infections of the ear canal are usually bacterial (staphylococci and gram-negative rods) although a few are caused by fungi (*Aspergillus*, *Mucor*, *Penicillium*).

Predisposing factors are moisture in the ear canal in a warm, moist climate or due to swimming or bathing and trauma due to attempts to clean or scratch the itching ear.

#### Clinical Findings

**A Symptoms and Signs.** Itching and pain in the dry, scaling ear canal are the chief symptoms. There may be a watery or purulent discharge and intermittent deafness. Pain may become extreme when the ear canal becomes completely occluded with edematous skin. Preauricular, postauricular, or cervical adenopathy or fever indicate increasing severity of infection.

Examination shows crusting, scaling, erythema, edema and pustule formation. Cerumen is absent. There may be evidence of seborrheic dermatitis elsewhere.

**B Laboratory Findings.** The WBC may be normal or elevated.

**C Special Examinations.** After the canal is cleansed so that the eardrum is visible, otitis media can often be excluded if tuning fork tests indicate normal or nearly normal hearing.

#### Treatment

**A Systemic Treatment.** If there is evidence of extension of infection beyond the skin of the ear canal (lymphadenopathy or fever), systemic antibiotics may be necessary. Systemic analgesics are required for pain.

**B Local Treatment.** The objectives of local treatment are to keep the ear canal clean and dry and to protect it from trauma. Debris may be removed from the canal by gently wiping it with a cotton applicator or with suction or occasionally irrigation. Glycerite of peroxide with urea ear drops is often helpful to remove debris.

Topical antibiotic ointments and ear drops (e.g., neomycin, polymyxin, bacitracin) applied to the ear canal with a cotton wick for 24 hours followed by the use of ear drops twice daily help to control infection. Topical corticosteroids aid in decreasing inflammatory edema and controlling the often underlying dermatitis. Many antifungal and antimicrobial agents may be used topically, but some must be used with caution because of the possibility of local sensitivity reactions. Compresses of Burrow's solution or 0.5% acetic acid are sometimes effective against acute weeping infected eczema when other measures fail. Severely pruritic alcohol frequently controls itching in the dry, scaling ear canal.

**Prognosis**

External otitis is often refractory to treatment, and recurrences are frequent.

Gill, E. K. Evaluation of treatment in external ear infections *Laryngoscope* 70 968-72, 1960

**DISEASES OF THE MIDDLE EAR****1. ACUTE OTITIS MEDIA****Essentials of Diagnosis**

- Ear pain *a sensation of fullness in the ear* and hearing loss aural discharge
- Onset following an upper respiratory infection
- Fever and chills

External otitis with pain fever and otorrhea may simulate otitis media Hearing loss and a history of a preceding upper respiratory tract infection are prominent with otitis media Nearly normal hearing and a history of itching are frequent with external otitis

**General Considerations**

Acute otitis media most commonly occurs in infants and children but it may occur at any age Suppuration of the middle ear usually occurs following or accompanying disease of the upper respiratory tract Beta-hemolytic streptococci, staphylococci pneumococci and Hemophilus influenzae are the usual infecting organisms The acute inflammation of the middle ear mucosa is followed by acute suppuration and then a more severe suppuration with perforation of the tympanic membrane and occasionally with necrosis of the middle ear mucosa and eardrum

**Clinical Findings**

**A Symptoms and Signs** The principal symptoms are ear pain deafness, fever chills and a feeling of fullness and pressure in the ear The eardrum at first shows dilatation of the blood vessels on the malleus and at the annulus, this is followed by diffuse dullness and hyperemia of the eardrum and loss of normal landmarks (short process of malleus) and bulging of the drum as the pressure of retained secretions increases in the middle ear If the eardrum ruptures, discharge is found in the ear canal, the discharge may be pulsating Fever is usually present

**B Laboratory Findings** The WBC is usually increased Culture of the drainage will reveal the infecting organism

**C Special Examinations** Hearing tests will show a conductive hearing loss

**Differential Diagnosis**

Acute otitis media with drainage must be distinguished from acute external otitis The history of a preceding upper respiratory tract infection and hearing loss confirm the diagnosis of otitis media Acute exacerbation of a chronic otitis media is diagnosed by a history of otorrhea and hearing loss and by finding scar tissue on the eardrum Reflex otalgia (pharyngitis laryngitis dental disease, temporomandibular joint disease) is present if there are no acute inflammatory changes in the ear canal or eardrum and no fever

**Complications**

Acute mastoiditis may occur as a complication

**Treatment**

**A Systemic Treatment** Bed rest analgesics and systemic antibiotics are usually required Penicillin or a broad spectrum antibiotic is usually the drug of choice and should be continued for at least 6 days to minimize the likelihood of recurrence of an incompletely resolved infection after a latent period

**B Local Treatment** Ear drops are of limited value except in the mildest cases Local heat may hasten resolution Local cold applications relieve pain occasionally The most important aspect of treatment is myringotomy when the infection does not resolve promptly or when bulging of the eardrum indicates that a discharge is present and is under pressure Myringotomy should also be promptly performed if there is continued pain or fever increasing hearing loss or vertigo

**Prognosis**

Acute otitis media adequately treated with antibiotics and myringotomy if indicated resolves with rare exceptions Complicating mastoiditis occurs most commonly following inadequate or no treatment Persistent conductive hearing loss with or without middle ear fluid may occur following incomplete resolution of the infection It is imperative to examine the ears and to test the hearing after otitis media to prevent persistent conductive hearing loss with serous otitis media or "glue ear"

## 2 CHRONIC OTITIS MEDIA

Chronic inflammation of the middle ear is nearly always associated with perforation of the eardrum. It is important to distinguish the relatively benign chronic otitis associated with eustachian tube disease - characterized by central perforation of the eardrum and often mucoid otorrhea occurring with an upper respiratory tract infection - from the chronic otitis associated with mastoid disease that is potentially much more dangerous. The latter is characterized by perforation of Shrapnell's membrane or posterior marginal perforation of the eardrum, often with foul smelling drainage and cholesteatoma formation. Drainage from the ear and impaired hearing are frequent symptoms.

Treatment of the chronic "tubal ear" should be directed at improving eustachian tube function by correcting nasal or sinus infection, infected or hypertrophied tonsils or adenoid, or nasal polyps or deviated nasal septum. Ear drops (alcohol and boric acid or antibiotic solutions) or dusting powders (iodine, boric acid or antibiotics) and frequent cleansing of the ear are of value. Systemic antibiotics have limited value. If there is evidence of continued suppuration or if mastoiditis or other complications occur, radical or modified radical mastoidectomy should be done. In some cases of chronic otitis media where hearing loss has occurred - and if the middle ear infection is quiescent and eustachian tube function is adequate - reconstructive middle ear operations (tympanoplasty) can be attempted to improve the hearing.

Hill, F. T. Comprehensive care in the treatment of chronic suppurative otitis media. *Laryngoscope* 71: 527-25, 1961.

## 3 SEROUS OTITIS MEDIA

Serous otitis media may occur at any age. It is characterized by the accumulation of sterile fluid (serous or mucoid) in the middle ear, producing symptoms of hearing loss, a full plugged feeling in the ear, and an unnatural reverberation of the patient's voice. It may be caused by (1) an obstruction of the eustachian tube which prevents normal ventilation of the middle ear and subsequent transudation of serous fluid, (2) an incompletely resolved exudate of purulent otitis media, or (3) an allergic exudate of serous fluid into the middle ear.

Examination shows a conductive hearing loss and a retracted eardrum, often with a characteristic "ground glass" amber discoloration. Air-fluid bubbles or a fluid level can sometimes be seen through the eardrum.

The absence of fever, pain, and toxic symptoms distinguish serous otitis media from acute otitis media. Cancer of the nasopharynx must be ruled out in persistent unilateral serous otitis media in an adult.

Local treatment consists of eustachian tube inflations, paracentesis of the eardrum with aspiration of the middle ear contents, and nasal decongestants (0.25% phenylephrine nasal spray or phenylpropanolamine, 25-50 mg orally t.i.d.). Antihistamines should be given if there is any suggestion of contributing nasal allergy. Underlying factors must be corrected by tonsillectomy, adenoidectomy, control of nasal allergy, and treatment of nasal or sinus infection.

Hays, A. V. Adenoid revision: its importance in the treatment of serous otitis media in children. *Laryngoscope* 71: 1402-18, 1961.

## 4 MASTOIDITIS

Acute mastoiditis is a complication of acute suppurative otitis media. Bony necrosis of the mastoid process and breakdown of the bony intercellular structures occur in the second to third week. When this occurs there is evidence of continued drainage from the middle ear, mastoid tenderness, systemic manifestations of sepsis (fever, headache), and x-ray evidence of bone destruction.

If suppurative mastoiditis develops in spite of antibiotic therapy, mastoidectomy must be done. Acute mastoiditis is rarely seen since chemotherapeutic and antibiotic therapy has become available for the treatment of acute suppurative otitis media.

Chronic mastoiditis is a complication of chronic otitis media. If the disease occurs in infancy the mastoid bone does not develop cellular structure but becomes dense and sclerotic. Infection is usually limited to the antral area. However, x-ray findings of a sclerotic mastoid does not necessarily mean that a chronic infection is present, only that an infection was present in infancy and that as a result the mastoid air cells are not well developed. The presence of infection must be determined by clinical findings. In some cases of marginal perforation or Shrapnell's mem-

brane perforation (attic perforation) of the eardrum, cholesteatomas develop. Cholesteatoma is produced by the ingrowth of squamous epithelium from the skin of the external ear canal into the middle ear or mastoid, forming an epithelial cyst. Desquamation and laminated growth of the cyst may produce erosion of adjacent bone or soft tissue.

Antibiotic drugs are usually of limited usefulness in clearing the infection in chronic mastoiditis, but they may be effective in the treatment of complications. Many cases of chronic otitis media and mastoiditis can be managed by local cleansing of the ear and instillation of antibiotic powders or solutions. Other cases may require radical or modified radical mastoidectomy or tympanoplasty.

### COMPLICATIONS OF MIDDLE EAR INFECTIONS

#### Following Acute Suppurative Otitis Media & Mastoiditis.

A. Subperiosteal abscess following acute otitis media and mastoiditis is infrequent. Simple mastoidectomy is required.

B. Facial nerve paralysis developing in the first few hours or days after the onset of acute otitis media is due to edema of the nerve in the bony facial canal. Conservative treatment is usually indicated (antibiotics, myringotomy, supportive measures).

C. Meningitis, epidural, subdural, and brain abscess, and sigmoid sinus thrombosis are serious complications of suppurative otitis media and mastoiditis which may be masked by antibiotic drugs. Surgical treatment of the mastoid disease and its complications is required.

#### Following Chronic Otitis Media.

A. Acute exacerbations of chronic otitis media and mastoiditis may lead to meningitis, epidural, subdural, and brain abscess, and sigmoid sinus thrombosis, requiring antibiotic therapy and surgery.

B. Facial nerve paralysis is usually the result of direct pressure on the nerve by cholesteatoma or granulation tissue. Mastoidectomy and decompression of the facial nerve are necessary.

Eby, L.J.: Petrositis and lateral sinus thrombosis due to antibiotic resistant infections. *Laryngoscope* 71:1165-85, 1961.

## DISEASES OF THE INNER EAR

### 1. MÉNIÈRE'S SYNDROME (Paroxysmal Labyrinthine Vertigo)

#### Essentials of Diagnosis.

- Intermittent attacks of vertigo, nausea, vomiting, profuse sweating
- Progressive, often unilateral nerve type hearing loss and continuous tinnitus.

Distinguish the vertigo from that produced by posterior fossa tumors (other findings such as papilledema, increased CSF pressure and protein, and brain stem signs). Differentiate dizziness and lightheadedness from those seen in some systemic diseases, brain stem vascular disease, and psychiatric disorders.

#### General Considerations.

Ménière's syndrome is characterized by recurrent episodes of severe vertigo associated with deafness and tinnitus. It is encountered most often in men in the age group from 40 to 60. The cause is not known, but "endolymphatic hydrops" with marked dilatation of the cochlear duct is the pathologic finding. Ménière's syndrome may follow head trauma or middle ear infection, but many cases develop without apparent damage to the nervous system or ear.

#### Clinical Findings

Intermittent severe vertigo, which may appear to throw the subject to the ground, is the principal symptom. Brief loss of consciousness occasionally occurs in an attack. "Spinning" of surrounding objects is often noted. Nausea, vomiting, and profuse perspiration are often associated. The attacks may last from a few minutes to several hours. The frequency of attacks varies considerably even in the same patient. Headache, nerve type hearing loss, and tinnitus occur during and persist between attacks. Hearing loss is apt to be progressive, and is unilateral in 90% of cases. Nystagmus may occur during attacks of vertigo. An altered labyrinthine response is often demonstrated by means of the caloric or Bárány test. There is increased sensitivity to loud sounds. Audiometric tests show recruitment, decreased speech discrimination, and a nerve type hearing loss.

## 2 CHRONIC OTITIS MEDIA

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1111, 1-1 Comprehensive care in the treatment of chronic suppurative otitis media. *Laryngoscope* 71 587-95 1961

## 3 SEROUS OTITIS MEDIA

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Hays A V Adenoid revision. Its importance in the treatment of serous otitis media in children. *Laryngoscope* 71 1402-18, 1961

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#### 4. ACUTE SUPPURATIVE LABYRINTHITIS

Acute suppurative labyrinthitis is an infection of the intralabyrinthine structures. It may occur following acute otitis media and mastoiditis, acute exacerbations of chronic otitis media and mastoiditis, or meningitis unrelated to ear diseases. There is usually total destruction of labyrinthine function in the affected area and complete unilateral deafness.

Antibiotics and surgical drainage are indicated.

#### 5. CHRONIC LABYRINTHITIS

Chronic labyrinthitis is secondary to erosion of the bony labyrinthine capsule (usually the lateral semicircular canal) by cholesteatoma. The patient has chronic episodes of vertigo, and attacks of vertigo can be reproduced by increasing the air pressure in the ear canal with a pneumatic otoscope (positive fistula test).

Mastoidectomy and removal of the cholesteatoma are required.

### DISEASES OF THE NOSE

#### VESTIBULITIS

Inflammation of the nasal vestibule may occur as a dermatitis of the skin of the nose, often as a result of irritation from a nasal discharge, as a fissure resulting from chronic dermatitis or the trauma of picking or wiping the nose, or as a furuncle, usually after pulling hairs from the nose. Symptoms vary from scaling and weeping to edema, hyperemia, intense pain, and abscess formation. Fissures usually occur at the junction of the columella with the ala or with the floor of the nose. Careful cleansing of nasal discharge, avoidance of pulling nasal hairs, and protection with petrolatum or boric acid ointment may prevent these problems.

The application of soothing, protective, and antimicrobial ointments (e.g., 5% ammoniated mercury, 3% tetracycline hydroxyquin cream, neomycin, polymyxin, or bacitracin ointments) several times daily for several

days after symptoms disappear is usually adequate treatment. For more severe infections, systemic antibiotics, local heat, and general supportive measures may be necessary.

#### NASAL SEPTAL HEMATOMA & ABSCESS

Septal hematoma occurs following trauma to the nose. The swollen septum produces nasal obstruction and frontal headache. Septal abscess usually is the result of an infected septal hematoma. It may occur following a furuncle in the vestibule, and produces nasal obstruction, headache, fever, malaise, pain in the nose, and tenderness over the nasal dorsum.

Septal hematoma may be treated conservatively by observation for possible infection; it should resolve in 4-6 weeks. It may also be relieved by aspiration with a large-bore needle or by incision and drainage, in both cases taking extreme precautions to prevent infection.

Septal abscess must be drained by wide incision of one side of the septum and suction. Necrotic pieces of cartilage may be cautiously removed. The incision must be wide enough to prevent early closure or must be spread open daily. Nasal packing may be necessary to control bleeding. Systemic antibiotics are required.

Destruction of cartilage causes saddle deformity.

Fearon, B., McKendry, J.B., & J. Parker. Abscess of the nasal septum in children. Arch Otolaryng. 74:408-12, 1961.

#### "COMMON RESPIRATORY DISEASE" (Common Cold, Grippe, Acute Bronchitis, Tracheobronchitis)

This group of diseases includes the numerous self-limited probably viral infections of the upper respiratory tract. Children 1-5 years old are most susceptible, and adults from 25 to 35 next most susceptible. The incidence is lowest during the summer months. Exposure to cold, chilling and dampness are probably of little etiologic significance.

Known viruses which may cause this syndrome are adenovirus, ECHO virus, Coxsackie virus, Influenza viruses, and Eaton virus. Many viral agents which probably cause the disease remain unidentified.

**Clinical Findings**

**A Symptoms and Signs** The patient complains of malaise, feverishness, with usually little or no fever, and headache. Nasal discomfort (burning, fullness, itching) is a prominent feature, with watery discharge and sneezing followed shortly by mucoid to purulent discharge and nasal obstruction. Throat symptoms include dryness, mild to moderate soreness, rather than actual pain, hoarseness, and tickling. Cough with scanty sputum and substernal aching may occur. Serious obstruction may occur in infants and young children or in adults with underlying bronchopulmonary disease (e.g., emphysema).

The nasal mucosa is reddened and edematous. The external nares are red. The pharynx and tonsils usually show mild to moderate injection without edema or exudate. Cases of pharyngitis with considerable injection and exudate which fail to yield beta hemolytic streptococci on repeated culture should probably be included in this group.

Cervical lymph nodes may be enlarged and slightly tender. Herpes labialis is common.

**B Laboratory Findings** The WBC may be slightly elevated, but in most cases this is due to secondary bacterial infection.

**Differential Diagnosis**

Many specific infectious diseases present initial manifestations indistinguishable from those of common respiratory disease. Vigilance is required to avoid diagnostic errors of omission (e.g., meningococcal infection, diphtheria).

Influenza is recognized by its epidemic occurrence and by serologic confirmation.

Exanthematous diseases (especially measles and chickenpox) may simulate common respiratory disease in the preeruptive phase.

Beta hemolytic streptococcal pharyngitis may be clinically indistinguishable from acute nonstreptococcal exudative pharyngitis. Cultures make the diagnosis.

**Complications**

Complications result from secondary bacterial infections, often aided by the obstruction of respiratory passages (e.g., sinusitis, bronchioles). They include purulent sinusitis or "maxillary" bacterial pneumonitis and tonsillitis.

**Treatment**

No specific treatment is available. Antibiotics are used only to prevent secondary infection in patients with low pulmonary and cardiac reserves and to treat complicating secondary infections.

General measures consist of rest, sufficient fluids to prevent dehydration, and a light, palatable, well-balanced diet. Aspirin may be given for headache, sore throat, muscle soreness, and fever. Vasoconstrictors give temporary relief of nasal obstruction and rhinorrhea. Phenylephrine hydrochloride (Neo-Synephrine®) 0.25% several drops in each nostril every 2-3 hours, or phenylpropanolamine hydrochloride (Propadrine®) 25-50 mg every 4-6 hours is satisfactory for this purpose. Antihistamines may relieve the early symptoms of mucous membrane inflammation. Cough may be reduced by inhaling steam or with codeine phosphate 8-15 mg ( $\frac{1}{8}$ - $\frac{1}{4}$  gr) orally every 2-4 hours. Heat to the area of the sinuses may relieve nasal obstruction.

Fuchs A M Differential diagnosis of the common cold. Eye Ear Nose & Throat Month 38 129 36 1959  
Kneeland Y Jr Common upper respiratory infection including the common cold. M Clin North America 43 1327 34 1959

## ALLERGIC RHINITIS (Hay Fever)

**Essentials of Diagnosis**

- Watery nasal discharge, sneezing, itching eyes and nose
- Pale, boggy mucous membranes
- Eosinophilia of nasal secretions and blood

A history of an allergy aids in distinguishing allergic rhinitis from the common upper respiratory infections. Hay fever should be suspected in young children as the real cause of repeated colds.

**General Considerations**

See discussion under Bronchial Asthma.

**Clinical Findings**

**A Symptoms and Signs** The principal symptoms are nasal congestion, a profuse watery nasal discharge, itching of the nasal mucosa leading to paroxysms of violent sneezing, conjunctival itching and burning, and lacrimation. The nasal mucosa are pale blue and boggy. Polyps may be present. The conjunctivas are often reddened and swollen.

**B Laboratory Findings** A smear of the nasal increased numbers of

eosinophils. (In infections, neutrophils predominate.) The peripheral blood may reveal mild (5-10%) or occasionally marked (30-40%) eosinophilia, even between clinical episodes.

Skin tests may be of aid in the detection of the allergens but must be correlated with the clinical picture to determine their significance.

#### Treatment.

**A. Specific Measures** There is no true specific treatment. Hyposensitization or desensitization is sometimes beneficial and consists of administering the allergen (usually pollen) in gradually increasing doses to induce an "immunity." For best results, therapy should be started 3-6 months before the beginning of the hay fever season.

#### B. General Measures

1. Antihistamines give relief in 60-80% of patients, but their effectiveness often wanes as the season continues.

2. Sympathomimetic drugs such as ephedrine and phenylpropanolamine are effective by themselves or in combination with the antihistamines.

3. Sedation may be of value for tense or nervous patients.

4. The corticosteroids are useful in severe hay fever which cannot be controlled by the agents mentioned above. Prednisone, 20-40 mg. by mouth daily in divided doses, may be used for several days until symptoms are controlled. Dosage should then be reduced gradually (over a period of 7-10 days) to the smallest daily dose that will suppress symptoms. Discontinue steroid therapy as soon as possible.

5. Maintenance of an allergen-free atmosphere and the use of dust-proof respirator masks and room air filters are often of value during the pollen season if the patient must remain in the area. When dust is the offending agent, prepare a dust-free bedroom as follows: Cover the mattress and pillow with an air-tight nonantigenic material (plastic or sheet rubber). Remove all carpets, drapes, bedspreads, and other lint-producing materials, and all ornate furniture or other objects which are not easily dusted. Blankets should be of synthetic material if possible.

Household pets must be considered possible sources of allergens.

#### Prognosis

Allergic rhinitis is a self-limited though recurrent disorder with mild morbidity and no mortality.

Missal, S. C.: Food allergy in the ear, nose & throat practice of allergy. Laryngoscope 71 512-23, 1961.

## SINUS INFECTION

#### Essentials of Diagnosis: Acute.

- History of acute upper respiratory infection, dental infection, or nasal allergy
- Pain, tenderness, redness, swelling over the involved sinus
- Nasal congestion and purulent nasal discharge
- Clouding of sinuses on x-ray or transillumination
- Fever, chills, malaise, headache
- Teeth hurt or feel "long" (maxillary sinusitis), or swelling occurs near the nasal canthus of eye (ethmoid sinusitis)

#### Essentials of Diagnosis: Chronic.

- Nasal obstruction
- Postnasal discharge
- Clouding of sinus on x-ray or transillumination
- Psin is not a common finding

*Acute sinusitis must be distinguished from acute rhinitis, dental infection (maxillary), blocked tear duct (ethmoid), and osteomyelitis of skull bones. The complaint of nasal obstruction must be distinguished from nasal allergy, vasomotor rhinitis, deflected nasal septum, nasal polyps, and tumor.*

#### General Considerations.

Acute sinus infection usually follows an acute upper respiratory infection, swimming or diving, dental abscess or extractions, or nasal allergies, or occurs as an exacerbation of a chronic sinus infection. Isolated acute frontal sinus infection is rare. Acute ethmoiditis is most common in infants and children. Chronic pyogenic infections of single sinuses do occur, but this is less common than pansinusitis.

#### Clinical Findings.

##### A. Symptoms and Signs

1. Acute sinusitis - The symptoms resemble those of acute rhinitis but are more severe. There is headache and facial pain, tenderness and swelling with nasal obstruction, and a purulent nasal and postnasal discharge, sometimes causing sore throat and cough. The headache typically is worse during the day and subsides in the evening. Acute maxillary sinusitis may cause pain in the teeth and a feeling of "long teeth." Acute ethmoiditis causes headache between and behind the eyes,

and eye motion increases the pain. Tenderness medially in the roof of the orbit occurs with frontal sinusitis. Fever and systemic symptoms vary with the severity of the infection.

**2 Chronic sinusitis** - Chronic sinus infection may produce no symptoms. A mild postnasal discharge and a musty odor or non-productive cough may be the only symptoms. Nasal obstruction and sometimes profuse purulent nasal and postnasal discharge may also occur.

**B Laboratory Findings** In acute sinusitis the WBC may be elevated and culture of nasal discharge usually shows the pyogenic organisms.

**C X-ray and transillumination** show clouding of the involved sinuses.

#### Differential Diagnosis

Acute dental infection usually produces greater facial swelling lower in the face with more marked tenderness of the involved tooth than does maxillary sinusitis. The more localized swelling and tenderness and greater involvement of the eyelids with absence of nasal discharge distinguishes an infected tear sac from ethmoiditis. X-ray examination gives more definite evidence of sinus involvement.

An isolated chronic maxillary sinusitis without obvious underlying cause suggests dental disease or neoplasm.

#### Complications

Chronic sinusitis is the commonest complication of acute sinusitis. Orbital cellulitis and abscess may follow ethmoiditis or frontal sinusitis. Frontal sinusitis may be complicated by meningitis or extradural subdural or brain abscess. Osteomyelitis of the facial or frontal bones may occur.

#### Treatment

**A Acute Sinusitis** Place the patient at bed rest and give sedatives, analgesics, a light diet and fluids. Oral nasal decongestants (e.g., phenylpropanolamine 25-50 mg t.i.d.) and systemic antibiotics frequently produce prompt resolution of the infection. Broad-spectrum antibiotics appear to be most beneficial but nearly all antibiotics have been effective.

**Local heat**, topical nasal decongestants (e.g., 0.25% phenylephrine) and gentle spot suctioning of the nasal discharge are helpful.

The sinuses must not be manipulated during the acute infection. Antrum irrigation

is of value after the acute inflammation has subsided. Acute frontal sinusitis is treated medically and conservatively; cannulation is rarely warranted. Trephining of the sinus floor may occasionally be indicated in acute fulminating infections. Acute ethmoid infections respond to medical management, if external fluctuation develops incision and drainage is indicated.

**B Chronic Sinusitis** When the infecting organism has been identified the suitable antibiotic is given systemically. Irrigation of the antra or Froetz displacement may help drainage. Conservative surgery to promote drainage is of value (removal of polyps, submucosal resection of an obstructing septum, intranasal anotomy). If conservative treatment is not effective, more radical sinus surgery by the external approach may be considered.

#### C Treatment of Complications

**1 Osteomyelitis, meningitis, abscess** - Give supportive measures and antibiotics. Remove necrotic bone and drain abscesses as required.

**2 Orbital fistula** - Treat the underlying sinus disease and close the tract surgically.

**3 Oroantral fistula** - Remove underlying sinus infection by the Caldwell-Luc operation and close the tract.

**4 Mucocoeles (mucopyoceles)** - Surgical excision.

#### Prognosis

Acute infections usually respond to medical management and irrigation.

Chronic infections often require surgical correction. Chronic frontal sinusitis is especially likely to persist or recur.

Catlin, F. F., Reynolds, R. C., & L. E. Cluff

Some aspects of therapeutics in sinusitis

Laryngoscope 71:620-22, 1961

Daws, J. D. K. The management of frontal sinusitis and its complications. J. Laryng. & Otol. 75:297-344, 1961

## NASAL TUMORS

#### Benign Tumors

Angioma, fibroma, papilloma, chondroma and osteoma are the most common types of benign neoplasms of the nose and sinuses. Nasal tumors produce obstruction and nasal discharge when they become large enough. Severe epistaxis occurs with angioma. Second-

any infection may occur. Pressure atrophy of surrounding structures, widening of the nasal bridge, and displacement of the eye may occur. X-rays and biopsy usually establish the diagnosis.

Treatment consists of complete removal with permanent intranasal drainage of involved sinuses.

### Malignant Tumors

Many nasal malignancies originate in the sinuses and extend into the nose. Sarcoma and carcinoma occur. Symptoms and signs may not occur until late, the most common are obstruction, discharge, epistaxis, pain, swelling of the face, and diplopia. X-rays show clouding of the sinuses that may suggest infection, secondary infection is frequently present. Bony destruction may show on x-rays. Cytologic smears of antrum irrigation fluid and "cell buttons" may show malignant cells. Biopsy is diagnostic.

Surgical excision is usually the treatment of choice. Some cases may be treated by biopsy followed by x-ray therapy or, occasionally, surgery plus irradiation or cautery.

Barrett, J.H.: Benign tumors of the nasal cavity. *South M.J.* 49:1311-6, 1956.

Devine, K.D.: Tumors of the nose and throat. *Arch. Otolaryng.* 73:80-124, 1961.

Lederer, F.L., & others: Tumors of the nasal cavity. *Laryngoscope* 67:592-604, 1957.

## EPISTAXIS (Nosebleed)

The most common sites of nasal bleeding are the mucosal vessels over the cartilaginous nasal septum (Kieselbach's area or Little's area) and the anterior tip of the inferior turbinate. Bleeding is usually due to external trauma to the nose, nasal infection (especially with vigorous nose-blowing), or drying of the nasal mucosa when humidity is low. Minor trauma such as nose-picking may lead to ulcerations of the nasal septum and subsequent hemorrhage. Up to 5% of nosebleeds originate posteriorly in the nose where the bleeding site cannot be seen, these can cause great problems in management.

Nosebleed may escape diagnosis if the blood drains into the pharynx and is swallowed. In these cases bloody or "coffee-ground" vomitus may be the first clue.

Underlying causes of nosebleed such as blood dyscrasias, hypertension, hemorrhagic disease, nasal tumors, and certain infectious diseases (measles or rheumatic fever) must be considered in any case of recurrent or profuse nosebleed without obvious cause.

### Treatment.

**A Specific Measures** Treatment of the underlying disease depends upon an adequate examination to detect cardiovascular, renal, or liver disease, blood dyscrasias, coagulation defects, or other systemic disorders contributing to the nosebleed. Give transfusions as necessary if blood loss is excessive.

**B Local Measures** Have the patient sit up and forward with his head tipped downward to prevent swallowing and aspiration of blood. Good illumination (with a head mirror or headlight) is essential to proper examination and treatment.

**1 Anterior epistaxis** - Pressure over the area (pinching the nose) for 5 minutes is often sufficient to stop bleeding. This may be combined with packing the bleeding nostril with a pledget of cotton moistened with hydrogen peroxide, 0.25% phenylephrine, or 1:1000 epinephrine solution.

After active bleeding has stopped (or if pressure fails to stop bleeding), a cotton pledget moistened with a topical anesthetic (1% tetracaine or 5% cocaine) applied to the bleeding area will provide anesthesia for cauterization with a chromic acid bead, trichloroacetic acid, or an electrocautery. After cauterization, lubrication with petrolatum helps prevent crusting. A second cauterization is infrequently necessary.

If the source of bleeding is not accessible to cauterization (beneath the inferior turbinate, behind septal spur, or high in the vault) or is not controlled by cauterization, the nasal cavity must be packed. After maximum shrinkage of the mucosa has been achieved with a suitable decongestant (0.25% phenylephrine or 2% ephedrine) and topical anesthesia, the nasal cavity can be tightly packed with half-inch gauze lubricated with petrolatum or cod liver oil. Pack the gauze into the nose in layers, starting either in the vault or on the floor of the nasal cavity. The packing may be left in place as long as 5-6 days if the patient is given adequate analgesics for pain and antibiotic medication to help prevent suppurative otitis media and sinusitis.

**2. Posterior epistaxis** - Posterior bleeding can sometimes be controlled only by means of a posterior nasal pack. This accomplishes 2 things: it compresses and controls bleeding.

sites in the nasopharynx or posterior choana and it provides a backstop for very firm anterior packing that might otherwise be dislodged in the pharynx.

The postnasal pack is prepared as follows (1) Sew 3 strings (No. 1 braided silk) through and through the center of a rolled 4 X 4 gauze sponge. (2) Pass a soft rubber catheter through the bleeding nostril into the pharynx and out through the mouth. (3) Attach 2 of the strings to the catheter tip and draw them through the mouth and out through the bleeding nostril. (4) Guide the gauze pack with a finger into the nasopharynx and posterior choana, taking care not to roll the uvula upward beneath the pack. (5) Anchor the 2 strings over a gauze bolster at the anterior nares. (6) Allow the third string to remain in the mouth and tape it to the face or cut it about 4 inches long and allow it to dangle in the pharynx. It is used later to remove the pack.

The pack should not be left in place more than 4 days. The patient's ears should be examined daily for evidence of acute otitis media. Bleeding may recur when the pack is removed or may even continue with the packing in place. If this occurs the pack must usually be changed or reinserted under general anesthesia.

If the bleeding persists beneath or behind an inaccessible nasal septal spur, submucous resection of the septum may be necessary to relieve traction on the mucosal vessels and to permit more effective packing.

If bleeding persists from a site low in the nasal cavity, external carotid artery ligation in the neck must be considered. Uncontrolled bleeding from high in the vault of the nose may necessitate ligation of the anterior or posterior ethmoidal artery (or both) as it passes from the orbit into the ethmoidal labyrinth.

#### Prognosis

Most anterior nosebleeds are easily treated as an office procedure. Complicated nosebleed or posterior nosebleed may require hospitalization for 2-3 weeks.

Severe nosebleed in cirrhotics or patients with borderline coronary arterial insufficiency may produce severe complications.

Beirfeld H H. General principles in treatment of nasal hemorrhage. *Arch Otolaryng* 57:519, 1953.

Quinn F B. Surgical treatment of nasal hemorrhage. *Arch Otolaryng* 54:734, 1960.

## DISEASES OF THE PHARYNX

### SIMPLE PHARYNGITIS

Acute simple (catarrhal) pharyngitis is an acute inflammation of the mucosa of the pharynx which to some extent involves the lymphatic structures also. It usually occurs as part of an upper respiratory tract disorder which may also affect the nose, sinuses, larynx, and trachea. The most common causes are bacterial or viral infection; rarely it is due to inhalation of irritant gases or ingestion of irritant liquids. Pharyngitis may occur as part of the syndrome of an acute specific infection (e.g., measles, scarlet fever, whooping cough).

The inflammation may be diffuse or localized (lateral pharyngitis). Drying of the mucosa occurs in pharyngitis sicca.

In acute pharyngitis the throat is dry and sore. Systemic symptoms are fever and malaise. The pharyngeal mucosa is red and slightly swollen, with thick, sticky mucus. The disease lasts only a few days.

Chronic pharyngitis may produce few symptoms, e.g., throat dryness with thick mucus and cough, or recurrent acute episodes of more severe throat pain, dull hyperemia, and mild swelling of the mucosa (especially the tonsil pillars), and thick tenacious mucus often in the hypopharynx.

The treatment of acute pharyngitis is symptomatic: rest, light diet, analgesics, and warm nonirritating gargles or throat irrigations. Antibiotics may be used for initial or complicating bacterial infection.

Chronic pharyngitis is treated by removing underlying causes such as infections of the nose, sinuses, or tonsils, and by restricting irritants such as alcohol, spicy foods, and tobacco. Local removal of the tenacious secretion with suction or saline irrigation and application of 2% silver nitrate are helpful.

### ACUTE TONSILLITIS

Acute tonsillitis is nearly always a bacterial infection, often due to streptococci. It is a contagious airborne or food-borne infection which can occur in any age group but is more common in children. Associated adenoidal infection in children is usual.

The onset is sudden, with sore throat, fever, chills, headache, anorexia, and mal-

aise. The tonsils are swollen and red; the tonsillar pillars and pharynx are red, and pus or exudate is present on the tonsils or in the crypts. The cervical lymph nodes frequently are tender and enlarged. The WBC may be elevated, and throat cultures will show the infecting organism.

Other causes of sore throat and fever which must be distinguished from acute tonsillitis include simple pharyngitis, infectious mononucleosis, Vincent's angina, diphtheria, sgranulocytosis, and mycotic infections. Smear and culture from the throat identify the bacterial and mycotic infections. The WBC helps distinguish viral infections and blood dyscrasias. The WBC and heterophil antibody titer will make the diagnosis of infectious mononucleosis.

The complications of local extension are chronic tonsillitis, acute otitis media, acute rhinitis and sinusitis, peritonsillar abscess or other deep neck abscess, and cervical lymph node abscess. Nephritis, osteomyelitis, rheumatic fever, or pneumonia may follow streptococcal tonsillitis.

Treatment consists of bed rest, fluids, a light diet, analgesics, and antibiotics as required. Local relief of pain may be obtained with frequent gargles or throat irrigations using hot, nonirritating solutions (e.g., saline, 30% glucose, aspirin).

Spontaneous resolution usually occurs after 5-7 days. Vigorous treatment may shorten the course, prevent many complications, and make the patient more comfortable.

## CHRONIC TONSILLITIS

Chronic tonsillitis usually results from repeated or unresolved acute infection. It is manifested by persistent dull hyperemia. Mild edema and scarring of the tonsils and tonsillar pillars may occur, and the crypts may contain abnormal secretions. Other symptoms and signs may range from a mild scratching sensation in the throat to cough, fetid breath, and a pharyngeal exudate. An enlarged cervical lymph node is common. The size of the tonsils is of little significance in determining the presence of chronic infection. Chronic infection may predispose to recurrent acute infections.

The treatment of significant chronic tonsillar infection is surgical excision (see below). Intercurrent acute infections and chronic infections in people who are poor operative risks (because of advanced age or severe systemic

or hemorrhagic diseases) are treated medically as outlined above for acute infections. Chronic infection can rarely be eradicated by conservative treatment.

### Adenotonsillectomy (T & A).

The value of adenotonsillectomy, the indications for and the contraindications to the operation, and the optimal time for the operation when it is indicated have been the subject of much controversy. Most surgeons agree that there are occasions when the operation is of definite benefit to the patient and that there are circumstances in which it is definitely contraindicated. Even when a strong indication for surgery is present, however, the decision to operate must not be made until all pertinent restraining factors (e.g., medical, psychological, social) have been evaluated.

Surgery is contraindicated during episodes of acute tonsillar infection. Many surgeons prefer to withhold the operation during the peak months of the poliomyelitis "season."

**A. Strong Indications.** Whenever the infected or hypertrophied tonsils and adenoid are almost certainly the underlying or only cause of the disease:

1. Recurrent acute infection or chronic infection of tonsils and adenoid
2. Recurrent acute ear infections
3. Persistent or recurrent serous otitis media
4. Peritonsillar abscess

**B. Equivocal Indications.** When the infected or hypertrophied tonsils are likely to be the cause of the disease or are contributing to or aggravating the disease (Other possible contributing factors must first be investigated and ruled out or treated.)

1. Snoring and mouth breathing
2. Large tonsils
3. Poor eating habits in a frail, often anemic child
4. Allergic rhinitis and asthma
5. Systemic disease, e.g., nephritis, rheumatic or congenital heart disease, rheumatic fever (considered a strong indication by some, even in the absence of local disease)
6. Frequent upper respiratory tract infections

**C. Relative Contraindications.** When the operation may do more harm than good unless special precautions are taken:

1. Cleft palate - Further speech impairment can occur following adenotonsillectomy. The lateral adenoidal masses only should be removed.

- 2 The mere presence of tonsils and adenoid
- 3 Systemic disease, e.g., uncontrolled diabetes, tuberculosis, heart disease
- 4 Intercurrent infection

**D. Absolute Contraindications** When the operation will certainly do more harm than good

- 1 Hemorrhagic disease, e.g., hemophilia
- 2 Far-advanced, severe systemic disease.

Timmons, I. M.: Tonsillectomy and adenoidectomy. Their relation to asthma in the allergic child. *Arch. Otolaryng.* 73 698-704, 1961.

### PERITONSILLAR ABSCESS (Quinsy)

Peritonsillar abscess is a complication of acute tonsillitis which occurs when the infection spreads into the potential peritonsillar space deep to the tonsil between the tonsillar capsule and the constrictor pharyngis muscle. Mixed pyogenic organisms (streptococci, staphylococci, pneumococci) are usually obtained upon culture. The sore throat of tonsillitis suddenly becomes more severe on one side when the infection breaks through the tonsillar capsule, dysphagia increases, trismus may be present, and one-sided swelling pushes the tonsil and tonsillar pillar toward or across the midline. The swelling extends to the soft palate, and the uvula is displaced. Fluctuation develops between the third and fifth days.

Symptomatic care and antibiotic therapy are indicated. After the abscess becomes fluctuant, it must be incised and drained. The walls of the abscess should be spread daily to prevent re-formation of the abscess. After the infection subsides, tonsillectomy should be done to prevent recurrences.

### LUDWIG'S ANGINA (Cellulitis of the Floor of the Mouth)

Ludwig's angina is a severe pyogenic infection of the sublingual and submaxillary spaces of the floor of the mouth and the anterior neck. A rapidly spreading diffuse cellulitis or abscess formation pushes the tongue upward against the roof of the mouth, limiting its motion and causing pain. The airway may become

obstructed, or the infection may spread downward in the neck.

Supportive treatment and large doses of antibiotics are necessary. If abscess occurs, external incision and drainage should be performed. Local anesthesia avoids the danger of immediate obstruction of the airway, which may occur if general anesthesia is used. Because of the diffuse nature of the infection, large quantities of free pus are seldom obtained. Incision must be adequate and the fascial spaces above and below the hyoglossus muscle must be opened by blunt dissection. A tracheostomy may be necessary.

### RETROPHARYNGEAL ABSCESS

Retropharyngeal abscess is a pyogenic infection which occurs most often in infants and children. Suppuration occurs in the fascial space between the posterior pharyngeal wall and the prevertebral fascia as a result of suppurative lymph node infection, usually following tonsillar, nasal, or sinus infection. The symptoms are difficulty in swallowing and breathing, and fever. The posterior pharyngeal wall is tender and swollen.

Early treatment (antibiotics, hydration) may produce resolution. If fluctuation occurs, incision and drainage are required, with the patient in full Trendelenburg position, adequate lighting and suction equipment at hand. General anesthesia is avoided because of the danger of laryngeal obstruction and aspiration. Tracheostomy may be necessary.

### PARAPHARYNGEAL ABSCESS

Parapharyngeal abscess is a pyogenic infection which occurs as a complication of acute tonsillitis, peritonsillar abscess, dental infection, or acute pharyngitis. It is localized in the fascial space outside the constrictor pharyngis muscle and deep to the investing cervical fascia, in close relationship to the carotid sheath and the stylopharyngeus and stylohyoid muscles. Infection can spread along the carotid sheath into the mediastinum. There are signs and symptoms of sepsis, bulging of the lateral pharyngeal wall, and trismus. The veins of the neck and scalp may be dilated as a consequence of pressure upon the jugular vein. Brawny swelling and redness may develop later in the neck below the angle of the mandible.



Early treatment consists of hydration and antibiotics in large doses. Intraoral incision and drainage should be done only by a surgeon familiar with this area because of the danger of hemorrhage from large blood vessels. External incision and drainage at the angle of the jaw and upper neck can be done if pus is sought deep in the neck by blunt dissection.

Caution is required in giving general anesthesia because of the hazard of airway obstruction. Local anesthesia or a tracheostomy for general anesthesia should be considered.

Harpman, J.A.: Parapharyngeal abscess of dental origin. *Eye Ear Nose & Throat Month*, 40:545-6, 1961.

## DISEASES OF THE LARYNX

### ACUTE LARYNGITIS

Acute inflammation of the laryngeal mucosa due to bacterial or viral infection may occur singly or in association with acute rhinitis, pharyngitis, or tracheitis. It may also occur with influenza, measles, or diphtheria, or as a result of inhalation of irritants. Hoarseness is the chief symptom. Pain and cough are often present. Stridor and dyspnea may occur if edema is marked. Examination of the larynx shows redness of the mucosa and edema with or without exudate. The acute inflammation may extend into the bronchi and lungs, and slight hemoptysis may occur if coughing ruptures small blood vessels.

Treatment consists of voice rest, decreased smoking, control of underlying nasal, sinus, or throat infections, and control of cough. Steam inhalations and local cold or heat to the neck may provide relief. Systemic antibiotics are helpful in bacterial infections. If marked edema produces dyspnea and stridor, parenteral steroids may decrease the edema sufficiently so that tracheostomy can be withheld.

### CHRONIC LARYNGITIS

Chronic inflammation of the laryngeal mucosa may be due to many causes, including repeated acute laryngitis, chronic vocal abuse, chronic inhalation of irritants (including smok-

ing), chronic sinus and throat infection, syphilis and tuberculosis (rare today), allergy, and hypometabolic states. Chronic hoarseness is the chief symptom. Cough, expectoration of tenacious secretions, and a feeling of dryness in the throat are often present. Examination shows signs of chronic inflammation, a thickened, dull, edematous mucosa of the vocal cords, and polypoid changes, whitish plaques, and thickened secretions. Ulceration is occasionally seen.

Chest x-ray and other tests for signs of tuberculosis, serologic tests for syphilis, and biopsy to rule out carcinoma may be required.

Treatment consists of correcting the underlying cause, if any, antibiotics for sinus and throat infections, antiallergenic measures when indicated, decreased smoking, and voice rest.

Gabriel, C.E., & D.G. Jones: The importance of chronic laryngitis. *J. Laryng. & Otol.* 74, 349-57, 1960.

Myerson, M.C.: Vocal rest in laryngeal disease. *Tr. Am. Laryng. A.* 79:31-7, 1958.

## TUMORS OF THE LARYNX

### Essentials of Diagnosis

- Hoarseness is the principal symptom
- Respiratory obstruction
- Sore throat, "sticking" sensation in throat, pain referred to the ear
- Cough or hemoptysis
- Dysphagia

Hoarseness and throat pain are frequent symptoms of acute laryngitis, upper respiratory infection, and influenza. Every patient with hoarseness need not be studied for laryngeal tumor, but hoarseness persisting longer than 2-3 weeks should be investigated at least by indirect laryngoscopy. Syphilis, laryngeal tuberculosis, granuloma, contact ulcers, asthma, and laryngeal paralyses also cause hoarseness.

### General Considerations.

Tumors of the larynx may be benign or malignant. Both produce similar symptoms and may be considered together. The symptoms depend upon the size and location of the tumor.

Benign laryngeal tumors may be neoplastic (e.g., papilloma, fibroma), may be due to allergy or metabolic disturbance (polyps), or

may be due to extrinsic or intrinsic trauma (singer's nodules, intubation granuloma). Ninety-five per cent of malignant laryngeal tumors are squamous cell carcinomas, but sarcoma, adenocarcinoma, and others occur

## TRACHEOSTOMY

### Clinical Findings.

Hoarseness is the earliest and principal manifestation of vocal cord tumor. As the tumor enlarges stridor and dyspnea may occur, usually late. With tumors elsewhere in the larynx (false cord, epiglottitis, aryteno-epiglottic fold, pyriform sinus) voice change may be a late symptom and minor throat discomfort (sometimes referred to the ear), dysphagia, or mild cough may be the only early symptoms. Laryngeal examination usually shows a mass or ulceration at the tumor site. Submucosal tumors may be manifested only as a fullness or swelling of the affected area. Biopsy examination establishes the diagnosis.

### Differential Diagnosis

Tumors of the larynx must be distinguished from chronic laryngitis, tuberculosis, syphilis, contact ulcer, granulomas, and laryngeal paralysis. Laryngeal symptoms lasting longer than 2-3 weeks must be investigated. Direct or indirect laryngoscopy is often diagnostic. Chest x-ray and other tests for tuberculosis, serologic tests for syphilis, laryngeal biopsy, and bacteriologic cultures usually establish a firm diagnosis.

### Treatment & Prognosis

Almost all of the techniques involved in intralaryngeal manipulation and surgery require the skills of an otolaryngologist.

Small, asymptomatic benign tumors may require no treatment other than diagnosis to rule out malignancy. Vocal cord polyps or ulcers due to metabolic disturbances (allergy or hypothyroidism) or to vocal misuse or other trauma may improve when the underlying problem is treated. Small benign tumors of the vocal cord producing hoarseness may be locally excised under direct or indirect laryngoscopy. Larger benign tumors - especially papillomas, which have a great tendency to recur - may require laryngotomy for adequate excision.

Malignant tumors are treated by external irradiation or surgical excision. Irradiation is suitable for superficial malignancies confined to the vocal cord which show no evidence of invasion of muscle or cartilage. More extensive tumors require surgical excision and often en bloc neck node dissection.

There are 4 indications for tracheostomy: (1) respiratory obstruction at the level of the larynx or above, (2) inability to clear tracheobronchial secretions, (3) for administration of anesthesia, and (4) to place the larynx at rest.

The causes of airway obstruction at or above the larynx include infections (laryngo-tracheobronchitis, epiglottitis, and diphtheria), tumors, edema (allergic, infectious, post-irradiation), trauma, and foreign bodies. Upper airway obstruction produces suprasternal, intercostal, and epigastric retraction and signs of hypoxia, including restlessness, increasing pulse, and, as a late finding, cyanosis. Disorders which interfere with normal sphincter action of the larynx permit aspiration of pharyngeal secretions, and prevent effective cough include loss of consciousness and organic muscular paresis due to poisoning, cerebrovascular accidents, postoperative state, poliomyelitis, and organic CNS disease. There are some surgical situations, especially in surgery of the head or neck, where an endotracheal tube cannot be introduced through the nose or mouth but can be introduced through a tracheostomy. Intralaryngeal disease rarely may require tracheostomy to place the larynx at rest.

Two kinds of tracheostomies are performed: emergency and elective. Emergency tracheostomy must be done immediately even if proper equipment and assistance is not available. In these circumstances, cricothyrotomy is a safe procedure which can be performed rapidly as follows. With a scissors or knife the skin is cut vertically over the cricothyroid membrane (the part of the airway nearest the skin), a transverse incision is made in this membrane, and the wound is spread with the knife handle or other dilator. It is essential to stay in the midline and to promptly replace this emergency airway with a proper tracheostomy. If a laryngoscope and endotracheal tube or a bronchoscope are available, the airway may be established with one of these devices and a deliberate tracheostomy then performed.

Elective tracheostomy is done under general or local anesthesia while the patient's airway is still adequate or has been reestablished with an endotracheal tube or bronchoscope. The precise surgical technique may vary, e.g., with midline or horizontal incision.

Work, W. L., & W. F. Boyle. Cancer of the larynx. *Laryngoscope* 71:830-46, 1961.

blunt or sharp dissection, retraction or division of the thyroid isthmus, but the principles are the same in all (1) avoid trauma to the cricoid cartilage, (2) stay in the midline to avoid trauma to lateral neck structures, and (3) do not close the incision tightly, thus minimizing subcutaneous emphysema.

Post-tracheostomy care must include humidifying the inspired air to keep secretions loose and prevent the formation of mucus plugs and crusts, frequent cleaning (every 2-4 hours) of the inner tube, avoidance of heavy sedation, and constant attention during the first 24-48 hours. Uninterrupted observation may not be necessary with some adults, but with small children it is absolutely necessary that a nurse, hospital attendant, or member of the family be in constant attendance as long as the tracheostomy is maintained.

Atkins, J. P.: Current utilization of tracheostomy as a therapeutic measure. *Laryngoscope* 70:1672-80, 1960.

## FOREIGN BODIES IN THE AIR & FOOD PASSAGES

Foreign bodies may lodge in the larynx, bronchi, or esophagus, usually while eating, following sudden inspiration caused by surprise, as a result of simple carelessness while holding something in the mouth, or while unconscious. Eighty per cent of cases of inhaled or swallowed foreign bodies occur in children under 15 years of age. In adults most foreign bodies are large boluses of food or bones lodged in the esophagus as a result of hasty eating or full dentures which impair normal sensation in the mouth.

Esophageal foreign bodies are usually found at the thoracic inlet, less commonly at the cardia or midesophagus. If laryngeal foreign bodies completely block the airway, asphyxia is imminent. A foreign body small enough to pass the glottis will seldom lodge in the trachea but will be found in the bronchi. The relatively sharp angle of the left bronchus and the straight right bronchus cause most bronchial foreign bodies to be found in the right side. Nearly all foreign bodies that enter food or air passages through the mouth and do not enter the stomach can be removed by the same route.

### Laryngeal Foreign Bodies.

Laryngeal foreign bodies may produce hoarseness, stridor, cough, and gagging; may obstruct the airway partially or completely and cause dyspnea, stridor, or asphyxia; and may produce inflammatory symptoms of fever, pain, tenderness, and swelling. They can be removed with a grasping forceps through a direct laryngoscope under topical or general anesthesia. The patient should be in the Trendelenburg position to prevent the foreign body from entering the trachea or esophagus, and a bronchoscope and esophagoscope of proper size should be available in case this happens.

A small laryngeal foreign body may become lodged in the bronchi (see below).

### Bronchial Foreign Bodies.

Bronchial foreign bodies usually produce an initial episode of coughing followed by an asymptomatic ("silent") period varying from a few hours (some vegetable foreign bodies) to months or years (less irritating nonvegetable foreign bodies) before obstructive and inflammatory symptoms occur (cough, wheezing, atelectasis, and pulmonary infection). If the foreign body lodges in such a way as to create a valve effect, obstructive emphysema of a pulmonary segment or lobe may be present. Recurrent episodes of cough and pulmonary infection, especially if unilateral, are suggestive of foreign body. X-rays will show a foreign body if it is radiopaque. Nonradiopaque foreign bodies will be revealed on x-ray only by the signs of bronchial obstruction and infection. Vegetable foreign bodies produce earlier and more severe inflammatory symptoms than nonvegetable objects.

In the differential diagnosis it is necessary to consider pneumonia, bronchiectasis, lung abscess, and tuberculosis.

Bronchial foreign bodies are removed through a bronchoscope with suitable forceps by a skilled endoscopist. General anesthesia is usually employed. In the case of very small radiopaque foreign bodies (e.g., straight pins) in the periphery of the lung which cannot be located with the bronchoscope alone, a biplane fluoroscope can sometimes be used. Thoracotomy is occasionally necessary to remove foreign bodies in the periphery of the lung.

Unrecognized bronchial foreign bodies may produce severe and progressive pulmonary infection, with pneumonia, abscess, and emphysema. In children, bronchoscopic manipulation may produce laryngeal edema severe enough to require tracheostomy.

**Esophageal Foreign Bodies**

Esophageal foreign bodies usually produce immediate symptoms of coughing and gagging pain in the neck at the level of the thyroid cartilage with a sensation of something stuck in the throat and difficulty in swallowing or inability to swallow food or saliva. Occasionally however especially in children weeks or months may pass before symptoms of infection or obstruction occur. Pooling of saliva in the pyriform sinuses is suggestive of esophageal obstruction. X rays will show opaque objects but often will not show a bolus of meat or a bone. Fluoroscopic observation as the patient swallows a capsule filled with barium sulfate or a wisp of cotton impregnated with barium sulfate is a useful means of locating suspected foreign bodies since the radiopaque test object will be delayed

by the foreign body in its transit through the esophagus.

Esophageal foreign bodies near the cardia may produce pain in the interscapular area.

Esophageal foreign bodies should be removed through the esophagoscope by a skilled endoscopist. Only rarely does an esophageal foreign body constitute an emergency and so the delay involved in referral is not usually hazardous. Blind probing in an effort to dislodge a foreign body is extremely hazardous.

Perforation of the esophagus by an esophageal foreign body or during endoscopic removal may lead to mediastinal infection (fatal in 50% of cases) or, rarely, severe hemorrhage.

Kaasay D. Observations on one hundred cases of bronchial foreign body. Arch Otolaryng 71:42-58, 1960.

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# Respiratory Tract & Mediastinum

R. Morton Monson, Sidney Levin, & Henry Broinard

## NONSPECIFIC MANIFESTATIONS

### Cough.

Cough is probably the most common symptom of respiratory disease. It may be produced by disturbances anywhere from the oropharynx to the terminal bronchioles. Cough may also occur in diseases not primarily respiratory in nature, e.g., congestive heart failure, mitral valve disease, otitis media, or subdiaphragmatic irritation. Patients often overlook or minimize a chronic cough, and detailed interrogation is sometimes necessary.

Paroxysmal cough suggests bronchial obstruction.

**Treatment of cough:** The best treatment for cough is to treat the underlying disease. The patient should avoid irritants such as smoking, allergens, dusts, fumes, and air pollutants. Bronchial spasm may be relieved with bronchodilating drugs given orally or by nebulization (or both). Antihistamines and, in severe cases, corticosteroids may be used to reduce inflammation of mucous membranes. (Newer corticosteroids suitable for topical use by nebulization are available, but experience with them is limited at present.) To liquefy tenacious sputum, give potassium iodide, saturated solution, 10-15 drops in water q.i.d. Antitussive drugs, e.g., codeine phosphate, 15-30 mg. (1/4-1/2 gr.) every 3-4 hours, or benzonatate (Tessalon<sup>®</sup>), 100 mg. every 3-4 hours, may be given as needed.

### Dyspnea.

Exertional dyspnea may appear with impaired ventilation (e.g., restrictive or obstructive defects), inefficient mechanics of breathing (e.g., high oxygen cost of breathing), or with diffusion defects. Early pulmonary disease seldom produces dyspnea.

Dyspnea at rest is more characteristic of congestive heart failure than of chronic pulmonary disease, but it does appear when secondary factors are superimposed on a low pulmonary reserve (e.g., bronchitis in an

emphysematous patient). Acute illnesses (pneumonia, spontaneous pneumothorax, bronchial asthma, massive plelectasis) can produce marked dyspnea at rest.

Orthopnea is usually considered to be presumptive evidence of congestive heart failure, but some pulmonary patients breathe easier in a sitting position (bronchial asthma).

### Expectoration.

The characteristics of the sputum must not be neglected. Mucoid sputum is seen in tracheobronchitis and asthma. A yellow or greenish sputum suggests bacterial infection. Foul-smelling sputum suggests anaerobic infection (e.g., putrid lung abscess). Pink, frothy sputum is seen in pulmonary edema. "Rusty" sputum is typical of pneumococcal pneumonia. Copious sputum separating into layers is characteristic of bronchiectasis.

The production of large amounts of sputum with a change of posture (e.g., upon arising in the morning) occurs when dependent cavities or bronchiectatic spaces suddenly empty into the bronchial tree.

### Wheezing.

Wheezing is the characteristic sign of bronchial narrowing. In bronchial asthma, it is paroxysmal and diffuse. Acute left ventricular failure may produce diffuse wheezing which is differentiated from asthma and bronchitis by associated signs of congestive failure and prolonged arm-to-tongue circulation time. A persistent localized wheeze is evidence of local bronchial obstruction (e.g., carcinoma, inflammatory stenosis, foreign body).

### Chest Pain.

Pain in the chest due to lesions of the respiratory tract occurs usually when lesions involve the parietal pleura. The central diaphragm refers pain to the neck, the peripheral diaphragm, to the upper abdomen. A "pleuritic" type of pain is frequently caused by diseases of chest wall structures (herpes zoster, intercostal nerve-root irritation, destructive neoplasms involving ribs). A localized bron-

chogenic carcinoma may produce a vague deep chest pain. Pain in the precordium usually indicates involvement of the myocardium or pericardium.

### Hemoptysis.

Bleeding from the lungs may occur in tuberculosis, bronchial carcinoma, adenoma, bronchiectasis, and chronic lung abscess. Fatal pulmonary hemorrhage is rare. Bleeding from the nose or pharynx may lead to a history of blood-spitting. Collateral circulation between the bronchial and pulmonary veins may cause hemoptysis in mitral stenosis. When associated with chest pain and shock, hemoptysis suggests pulmonary infarction.

### Cyanosis

Cyanosis represents increased concentration of reduced hemoglobin in the blood, which can result from a number of defects of function in pulmonary disease: (1) impaired diffusion from alveoli to capillaries; (2) inadequate gross ventilation of alveoli; and (3) disturbed perfusion-ventilation relationships (increased intrapulmonary "shunts").

Reduced hemoglobin in the blood may not be manifested as frank cyanosis even when present to a significant degree.

### Polycythemia.

Increase in the total erythrocyte mass may be very striking as a compensatory response to the chronic anoxemia of pulmonary insufficiency. Primary polycythemia (erythremia) is usually associated with a normal arterial oxygen saturation, but differentiation from the symptomatic variety is not always easy on this or any other basis.

Polycythemia is discussed on p. 292.

### Pulmonary Osteoarthropathy

Pulmonary osteoarthropathy refers to those changes in the bones and soft tissues of the extremities seen in some patients with chronic pulmonary disease. These include clubbing of the fingers and toes, subperiosteal proliferation in the long bones, arthralgia, and nonpitting edema of the skin. Such manifestations have been known to disappear with correction of the pulmonary pathology (e.g., resection of a localized bronchial carcinoma). The pathogenesis of pulmonary osteoarthropathy is not understood.

Clubbing is frequently seen in bronchiectasis, bronchial carcinoma, and lung abscess. It is unusual in tuberculosis. It may also be caused by such diverse nonpulmonary disorders as congenital heart disease and hepatic cirrhosis, and it may occur as a congenital trait.

## DISORDERS OF THE BRONCHI

### BRONCHITIS

Bronchial infection or inflammation is a prominent symptom of many pulmonary diseases (e.g., tuberculosis, bronchiectasis, emphysema), but its clinical importance in certain situations is often underemphasized.

Acute bronchitis is characterized by wheezing and associated musical rhonchi (or, less commonly, moist rales), productive (mucopurulent to purulent) cough, and absence of x-ray densities (apart from those due to underlying lung disease). It is common in viral infections (e.g., upper respiratory infection, measles), and in the healthy adult is rarely serious, but in infants and small children respiratory obstruction may be severe and life threatening. In the adult with chronic pulmonary insufficiency (especially emphysema), superimposed acute bronchitis may lead to critical impairment of ventilation and death. Sputum cultures may reveal a variety of bacteria (e.g., alpha- and beta-hemolytic streptococci, pneumococci, *Hemophilus influenzae*).

Chronic bronchitis is characterized by similar features of long duration without a clear prodrome of acute upper respiratory infection. Sputum cultures often fail to yield a definite bacterial pathogen. There is increasing evidence that cigarette smoking plays an important role. The obstruction caused by chronic bronchitis is generally thought to be a significant contributing factor in the pathogenesis of emphysema, with which chronic bronchitis is frequently associated.

### Treatment

**A. Acute Bronchitis.** Bed rest is advisable and smoking should be prohibited. Sufficient fluids should be provided to prevent dehydration. Steam inhalation is usually helpful. Ephedrine, 25 mg ( $\frac{3}{8}$  gr) orally, or isoproterenol hydrochloride (Isuprel<sup>®</sup>, Aludrine<sup>®</sup>), 1.200 by nebulization, is helpful if bronchial spasm is present. An antihistamine may help relieve bronchial inflammation. Severe cough should be controlled with codeine phosphate, 15-30 mg ( $\frac{1}{4}$ - $\frac{1}{2}$  gr) every 3-4 hours, or a comparable antitussive agent. Aspirin will help reduce fever and make the patient more comfortable. Antibiotics should be used in an attempt to prevent secondary infection in patients with impaired respiratory or cardiac function or debility from other ill-

ness, and in infants and children with severe symptoms. Sputum cultures are not usually helpful. Use penicillin procaine, 600,000 units i.m. b.i.d.; penicillin tablets, 400,000 units q.i.d.; penicillin V tablets, 250 mg q.i.d., or one of the tetracycline drugs, 250 mg q.i.d.

**B. Chronic Bronchitis:** The possibility that the "bronchitis" is secondary to some serious underlying disease must always be kept in mind. Sources of possible chronic irritation should be avoided (e.g., smoking, allergenic agents, fumes or other occupational hazards). A change of climate may sometimes be warranted. Nonproductive cough should be suppressed with codeine phosphate, 15-30 mg (1/4-1/2 gr.) every 3-4 hours, or a comparable antitussive agent. Bronchial spasm (frequently present with paroxysmal coughing) should be relieved with ephedrine sulfate, 8-25 mg (1/8-3/8 gr.), or related drugs, orally every 4 hours, or isoproterenol hydrochloride (Isuprel<sup>®</sup>, Aludrine<sup>®</sup>), 1:200 solution by nebulization every 2-4 hours. Both ephedrine and isoproterenol may be used. Bronchial inflammation may be reduced by the use of antihistamine drugs, in severe, intractable cases, the use of corticosteroid drugs such as prednisone is justified. Prednisone is given orally in an initial dosage of 5-10 mg q.i.d. for 3-4 days, and then gradually reduced to a small maintenance dose or, preferably, eliminated over the next 7 days.

Antibiotics are indicated if the sputum is purulent. Penicillin or one of the tetracyclines given orally are the drugs of choice. (See treatment of acute bronchitis for dosage.) If improvement does not occur in several days, sputum culture to determine the predominating organisms and antibiotic sensitivities may be helpful. After initial control is achieved, prolonged maintenance treatment with one-half the usual dosage may be necessary to prevent relapse.

Cardon, L., Lemberg, L., & R.S. Greenebaum: Acute suppurative bronchitis and bronchiolitis in chronic pulmonary disease: diagnosis and management. *Ann. Int. Med.* 34:559, 1951.

Fletcher, C.M.: Chronic bronchitis. Its prevalence, nature and pathogenesis. *Am. Rev. Resp. Dis.* 80:483-84, 1959.

Francis, R.S., & C.C. Spicer: Chemotherapy in chronic bronchitis - influence of daily penicillin and tetracycline on exacerbations and their cost. Report to Research Committee of British T.B. Association by their Chronic Bronchitis Subcommittee. *Brit. M.J.* 1:297-303, 1960.

## BRONCHIAL ASTHMA

### Essentials of Diagnosis.

- \* Recurrent acute attacks of wheezing, dyspnea, cough, and mucoid sputum.
- \* Prolonged expiration with generalized wheezing and musical rales.
- \* Eosinophilia of sputum and blood.

Distinguish wheezing from that due to bronchitis, obstructive emphysema, and congestive heart failure.

### General Considerations.

Familial susceptibility, environmental exposure, and such modifying factors as psychogenic stimuli must all be considered in the etiologic evaluation of an allergic patient. Half of these patients give a definite history of family allergy (rhinitis, asthma, eczema, urticaria). Seventy-five per cent of children with 2 allergic parents will be allergic. A familial history gives no information, however, about the specific clinical expression of the allergy.

Most allergic disorders of the respiratory tract are caused by inhalant allergens, principally pollens (especially the ragweed family), animal danders, and house dusts. The evidence for bacterial etiology ("intrinsic" asthma) is not convincing.

Modifying factors (psychic stress, infections, endocrine disturbances) may precipitate symptoms by upsetting the "balance" between the patient and his allergenic environment. The antigen-antibody reaction then results, and leads to the rapid appearance of reversible tissue changes: increased capillary permeability, increased secretion of mucus, spasm of smooth muscle, and increased numbers of eosinophils in the tissues, secretions, and peripheral blood.

The onset of bronchial asthma is usually before 20 years of age.

### Clinical Findings.

**A. Symptoms and Signs.** Bronchial asthma is characterized by recurrent acute attacks of wheezing, dyspnea, cough, and expectoration of mucoid sputum (especially at the end of an attack). Coughing at night, coughing and wheezing on exertion, and a history of frequent "colds" may be more prominent in children than clear-cut paroxysms of wheezing. Nasal symptoms (itching, congestion, and watery discharge) may precede attacks of wheezing.

The acute attack presents a characteristic picture. The patient sits up, "fighting for air," with his chest fixed in the inspiratory position and using his accessory muscles of respiration. Great difficulty is evident with expiration.

Wheezing may be audible across the room and usually overshadows other pulmonary signs. In the young asthmatic wheezing characteristically disappears or diminishes markedly soon after the injection of epinephrine.

When bronchial asthma becomes prolonged with acute severe intractable symptoms it is known as status asthmaticus.

**B Laboratory Findings** The sputum is characteristically tenacious and mucoid containing plugs and spirals. Eosinophils are seen microscopically. The differential count may show eosinophilia. (Skin testing is discussed in Chapter 20.)

**C X ray Findings** Chest films usually show no abnormalities. Emphysema may be acute (reversible) in severe paroxysms or chronic (irreversible) in long standing cases. Transient migratory pulmonary infiltrations have been reported. Pneumothorax may complicate severe attacks.

### Complications

Chronic bronchial asthma may lead to such complications as chronic pulmonary emphysema and chronic cor pulmonale. Other complications are atelectasis, pulmonary infection and pneumothorax.

### Treatment

The treatment may be divided into 2 phases: (1) Treatment of the acute attack and (2) Interim therapy which is aimed at preventing further attacks. Epinephrine and 1% aminophylline are the drugs of choice for the emergency management of acute bronchial asthma. However, for status asthmaticus or for acute attacks in epinephrine resistant patients, the adrenal corticoids and corticotropin are usually necessary. Intravenous hydrocortisone (Solu-Cortef®) is the preparation of choice. Corticotropin is equally effective, but the response is slower. Note: Epinephrine must be used cautiously in patients with cardiac asthma, hypertension or angina.

**A Treatment of the Acute Attack** Eliminate known allergens from the patient's environment. Maintain adequate rest and relieve apprehension by reassurance and sedatives. Treat respiratory infections vigorously with antibiotics. Give fluids orally or parenterally as necessary to prevent dehydration.

Of the expectorants available, only the lozides have demonstrated capacity to liquefy or increase the secretions of the lower respiratory tract. For this purpose potassium iodide saturated solution 10-15 drops in water q.i.d. is added to the treatment program.

1. Mild or moderate attack - Epinephrine is the drug of choice.

(1) Epinephrine Injection (1:1000) 0.2-0.5 ml subcut. For moderate attacks repeat every 1-2 hours.

(2) Epinephrine Inhalation (1:100) or Isoproterenol hydrochloride (Isuprel®) Inhalation (1:200 in aqueous solution) by nebulizer every 3-10 minutes p.r.n. Isuprel® is also available in tablets of 10 and 15 mg for sublingual administration, but most patients find inhalation therapy preferable because it is associated with fewer cardiovascular side effects. Isoproterenol microcrystals for inhalation are useful but are more expensive.

(3) Sterile epinephrine suspension (1:500 in oil) 0.2-1 ml i.m. may also be given at onset (and repeated in 10-14 hours p.r.n.) if a prolonged effect is desired.

(4) If the attack is not controlled with epinephrine or isoproterenol, give aminophylline 0.25-0.5 Gm (3 $\frac{3}{4}$ -7 $\frac{1}{2}$  gr) in 10-20 ml as follows: 1 V or 0.5 Gm (7 $\frac{1}{2}$  gr) added to 500-1000 ml of saline and given by I.V. drip. Aminophylline may also be given in solution rectally or as rectal suppositories.

(5) Ephedrine sulfate or hydrochloride 25-50 mg (3/8-3/4 gr) with or without a barbiturate may relieve mild attacks.

(6) Sedation: Phenobarbital 0.1 Gm (1 $\frac{1}{2}$  gr) stat. may repeat 0.03 Gm (1/2 gr) q.i.d.

2. Severe attack in epinephrine responsive patients (May also treat as for Status Asthmaticus below.) Use epinephrine, aminophylline and sedation as for a mild or moderate attack. Inhalations of 100% oxygen (or 80% oxygen with 20% helium) by mask at a rate of 6-12 L/min. may give great relief from dyspnea. When available, oxygen by intermittent positive pressure breathing (e.g. Bennett apparatus) and bronchodilating aerosols administered simultaneously through the same apparatus often afford relief. As a bronchodilator isoproterenol (Isuprel®) 1:400 is preferred because it produces fewer systemic reactions than epinephrine. IPPB may be used 15-20 minutes of every hour.

If the response to the above measures is not satisfactory, use I.V. hydrocortisone or corticotropin as described below.

Adequate hydration with I.V. fluids is very important in the treatment of severe asthma.

3. Status asthmaticus and severe attack in epinephrine resistant patients - Hospital treatment is mandatory, but relief of respiratory distress is the immediate objective of therapy before transportation. Give hydrocortisone sodium succinate (Solu-Cortef®) 100 mg i.v.



stat Add another 100 mg to 500 ml of 5% dextrose in water and begin a fairly rapid infusion. The rate of the infusion can be slowed when improvement is evident. The next most effective drug is corticotropin injection by I V drip 20-40 mg over a period of 6-8 hours. Simultaneously with the I V drugs give prednisone 5-10 mg orally every 6 hours. Relief should be evident in 6-12 hours and complete freedom from wheezing frequently occurs in 24-48 hours. The oral corticoid should be gradually eliminated over the following 7-10 days.

The patient should be hospitalized in an allergen free room. Inhalations of 100% oxygen (or 80% oxygen with 20% helium) should be given by mask for relief of dyspnea. Give aminophylline 0.25-0.5 Gm ( $3\frac{3}{4}$ - $7\frac{1}{2}$  gr) in 10-20 ml saline slowly I V and by rectal suppository for immediate relief of symptoms or 0.5 Gm ( $7\frac{1}{2}$  gr) may be added to 500 ml of normal saline and 5% dextrose in water given by I V drip.

Sedation must be adequate until relief is obtained. Use one of the following: Pentobarbital sodium 0.1-0.2 Gm ( $1\frac{1}{2}$ -3 gr) or paraldehyde 8-15 ml (2-4 dr) in 30 ml (1 oz) oil by rectum.

Adequate hydration is very important using I V fluids as necessary. It is best to give hydrocortisone or corticotropin infusions separately.

If hydrocortisone or corticotropin (ACTH) is not available administer epinephrine cautiously 1 ml of 1:1000 solution in 1 L of 5% dextrose by I V drip (60-80 drops/minute). If resistance continues a general anesthetic may be life saving. Give ether 30-90 ml (1-3 oz) in equal quantities of olive oil rectally and repeat in 12-24 hours if necessary. The patient usually awakens free of symptoms. If an anesthesiologist is available inhalation ether anesthesia may be employed.

Bronchoscopy under general anesthesia is sometimes indicated to remove tenacious secretions. Tracheostomy may be necessary to maintain a clear airway.

**B Interim Therapy** Attempt to identify the offending allergens and treat accordingly. Emotional disturbances should be eliminated if possible. Good living hygiene should be promoted. Patients with intrinsic asthma (usually due to infections of bronchi) may be helped by antibiotic therapy.

Ephedrine hydrochloride or sulfate 25-50 mg ( $3\frac{3}{8}$ - $3\frac{3}{4}$  gr) with or without phenobarbital 15-30 mg ( $1\frac{1}{4}$ - $1\frac{1}{2}$  gr) every 3-6 hours may prevent or reduce recurrences. The following is a useful prescription incorporating aminophylline.

Aminophylline ephedrine phenobarbital capsules

R Aminophylline	0.2	(3 gr)
Ephedrine hydrochloride or sulfate	0.025	( $\frac{3}{8}$ gr)
Phenobarbital	0.015	( $\frac{1}{4}$ gr)

Sig One capsule every 4 hours

Nebulized isoproterenol (Isuprel<sup>®</sup>) 1-200 from a pocket nebulizer is useful in controlling mild symptoms and preventing more severe episodes.

Antihistamines may give relief in some patients but their use in bronchial asthma has generally been disappointing.

Patients who are not helped by other measures may be treated on a long term basis with prednisone or a similar corticosteroid. The dosage employed should be just sufficient to keep the patient comfortable and relatively free of symptoms. Begin with 5 mg 3-4 times daily.

### Prognosis

Most patients with bronchial asthma adjust well to the necessity for continued medical treatment throughout life. Inadequate control or persistent aggravation by unmodifiable environmental conditions favors the development of incapacitating or even life threatening complications.

Curry J J Pathogenesis of bronchial asthma M Clin North America 34 1829 38 1950

Rackemann F M & M C Edwards Asthma in children A follow up study of 688 patients after an interval of twenty years New England J Med 246 815 23 and 858 63 1952

## BRONCHIECTASIS

### Essentials of Diagnosis

- Chronic cough with expectoration of large amounts of purulent sputum which separates into layers hemoptysis
- Rales and rhonchi over lower lobes
- X ray of chest reveals little bronchograms show characteristic dilatations

Differentiate from chronic tuberculosis which also may lead to bronchiectasis other causes of hemoptysis such as carcinoma and adenoma and acute pulmonary infections

### General Considerations

Bronchiectasis is a dilatation of the medium size bronchi with destruction of bronchial elastic and muscular elements. It may be caused by pulmonary infections (e.g. pneumonia, pertussis or tuberculosis) or by bronchial obstruction (e.g. due to neoplasms, foreign bodies or extrinsic pressure). Atelectasis and congenital defects in children (e.g. situs inversus, pulmonary cysts, absent frontal sinuses) are commonly associated with bronchiectasis.

Since infection and bronchial obstruction do not regularly produce significant bronchiectasis, unknown intrinsic factors are presumed to play a role. In 50-60% of patients a history of onset following a single pulmonary disease (usually in childhood) is obtained. Sinusitis is present in most patients, but its relation to the bronchial disease is not well understood.

### Clinical Findings

**A. Symptoms and Signs.** Symptoms arise as a result of impaired bronchial function (i.e. loss of expulsive and ciliary function) and stasis which permits secretions to accumulate in the dilated segments. The patient gives a history of a chronic productive cough and bronchitis-like symptoms associated with repeated bouts of pneumonia. The usual etiologic agents of pneumonia are found. (Delayed resolution of a pneumonia should always suggest underlying bronchial disease.) Chronic cough and expectoration are characteristic. Large amounts of purulent sputum which often separates into 3 layers (sediment, fluid, foam) on standing are produced. Expectoration is greatest with changes of posture (allowing sudden drainage of bronchiectatic segments) such as arising from bed.

Hemoptysis occurs in about 50% of cases. It is severe in 10-20% but is rarely fatal. Even in tuberculosis and bronchial neoplasm secondary bronchiectasis may be the main source of bleeding.

Weight loss, asthenia, night sweats, and fever are the result of chronic and acutely exacerbating pulmonary infection.

Pulmonary insufficiency may result from recurrent destruction of pulmonary tissue with resulting fibrosis and emphysema.

Rales and rhonchi over the lower lobes are the most prominent physical findings, and the diagnosis of bronchiectasis is uncertain if they are persistently absent. They are more frequently elicited if the examination is carried out before and after postural drainage with coughing (head down position). Retraction of the chest wall, diminished thoracic excursion, and mediastinal shift toward the side of major

involvement will be noted in long standing disease with loss of lung tissue. Varying signs of pneumonia are present during acute infection.

Emaciation, cyanosis, and clubbing of the fingers are seen in advanced cases, as with other chronic suppurative pulmonary diseases.

**B. Laboratory Findings.** Secondary polycythemia will be present in advanced disease. Sputum smears and cultures aid in the selection of appropriate antibiotics and help to rule out active tuberculosis (especially important in bronchiectasis of the upper lobe).

**C. X-ray Findings.** Plain chest films are at times helpful. Linear bands at times with club-shaped endings may be seen radiating from the hilar areas to the bases. Multiple annular shadows may appear along the heart borders. A collapsed lower lobe visible as a triangular density is sometimes noted.

Selective instillation of iodized dye into the bronchial tree (bronchograms) reveals sacculated, cylindrical or fusiform dilatations with loss of the normal tree in full bloom pattern of the terminal bronchi.

**D. Instrumental Examination.** Although bronchoscopy does not allow visualization of the bronchiectatic areas, it may reveal bronchial obstruction as the underlying pathology may identify pulmonary segments giving rise to sputum, and can be utilized for bronchography. Caution: Bronchographic examination is contraindicated during acute infections.

### Complications

Recurrent infection in poorly drained pulmonary segments leads to chronic suppuration and pulmonary insufficiency. Complications include severe or fatal hemoptysis, brain abscess, chronic cor pulmonale, and amyloidosis.

### Treatment

**A. General Measures.** Postural drainage is the most effective measure for the relief of bronchiectasis. The patient should assume the position that gives maximum drainage (usually prone across the bed with folded arms resting on a pillow on the floor), maintaining this position for 10-15 minutes 2-4 times a day. The first drainage is upon awakening and the last at bedtime.

Bronchoscopic drainage is of value initially to eliminate bronchial stenosis or obstruction. It may be necessary to dilate the stenosed bronchus, but repeated bronchoscopy is not advised.

Prompt attention to upper respiratory infections is very important in preventing bronchial infection. Many patients with bronchi

ectasis suffer from chronic upper respiratory tract infections with postnasal drip. This must be corrected whenever possible.

Although climate does not cure, a warm, dry climate often is of benefit, especially since it tends to reduce the incidence of upper respiratory infections. Avoid a dusty, smoke-filled atmosphere.

Patients with severe disease should have adequate rest in bed. The foot of the bed should be raised 6-12 inches. Good nutrition and health are very important. Smoking must be prohibited.

When resectional surgery is not feasible and a large sputum volume is present, a permanent tracheostomy or tracheal fistula may permit better drainage by frequent catheter aspiration.

**B. Specific Measures:** Antibiotic therapy reduces cough, sputum, and other symptoms, especially during acute exacerbations, but these benefits may be transient and the antibiotics are best used intermittently as exacerbations occur. Prolonged use of antibiotics in maintenance dosage (usually one-half the regular dose) is sometimes indicated.

1. Penicillin may be used parenterally (best for attacks of acute pneumonia), orally (best for prolonged use), or by aerosol, which is often very effective in doses of 50,000-100,000 units of sodium penicillin G in 1-2 ml. of physiologic saline solution, q.i.d.

2. Streptomycin aerosol may also be of benefit in some patients, especially those in whom penicillin resistance occurs. Each ml. should contain 50-250 mg. of streptomycin sulfate, depending upon the concentrations desired. Administer in the same manner as for penicillin (see above).

3. Combined penicillin-streptomycin aerosols are of benefit in many cases. Use the same concentrations for each drug as when used individually.

4. Tetracycline drugs, 250 mg. q.i.d. orally, or oxytetracycline (Terramycin®), 50 mg./ml. in propylene glycol by aerosol.

5. Enzymes - Pancreatic dornase (Dornase®), given by aerosol, may be of value in liquefying thick inspissated secretions.

**C. Surgical Treatment** Pulmonary resection is indicated (1) for younger patients in otherwise good health with recurring symptoms, and (2) for patients up to 60 years of age with severe symptoms (especially recurrent hemorrhage) due to predominantly unilateral disease who are otherwise good surgical risks. Modern surgery will permit resection of fairly extensive bilateral lesions if they are localized.

## Prognosis.

The judicious use of antibiotics and surgery has greatly improved the prognosis in bronchiectasis.

Lisa, J. R., & M. B. Rosenblatt. *Bronchiectasis*. Oxford, 1943.

# DISEASES OF THE LUNGS

## PNEUMOCOCCIC (LOBAR) PNEUMONIA

### Essentials of Diagnosis

- Sudden onset with shaking chills, fever, chest pain, and cough with rust-colored sputum.
- Involvement and consolidation are lobar in distribution.
- Leukocytosis.

Pulmonary infarction and pulmonary atelectasis may closely mimic pneumococcic pneumonia. Even when the diagnosis of pneumococcic pneumonia is established beyond doubt, the possibility of another lesion must be kept in mind (e.g., neoplasm, benign obstruction).

### General Considerations.

Pneumonia consists of inflammatory changes in the lung parenchyma which are almost always associated with or caused by infection. Pneumococcic pneumonia is due to *Diplococcus pneumoniae* infection and is characterized by consolidation of one or more lobes of the lung.

The occurrence of pathogenic types of pneumococci in normal individuals gives weight to the concept that the clinical disease represents a breakdown of normal resistance. Exposure to cold, malnutrition, alcoholism, and drug addiction are recognized predisposing features.

The usual age group is 30-50 years.

### Clinical Findings.

**A. Symptoms and Signs** Onset is usually sudden, with shaking chills, pleuritic chest pain (may be referred to abdomen, shoulders, or elsewhere), cough, fever to 40.6°C. (105°F.), and expectoration ("rusty," "prune-juice" sputum). There may be a recent history of minor respiratory illness.

The patient is severely ill, with marked tachypnea (30-40/minute) without orthopnea,

grunting respirations, use of accessory muscles of respiration, flaring of nares, and splinting of the chest (the patient lies on the affected side). Herpes labialis is frequently present. At onset thoracic excursion is decreased on the involved side. Breath sounds are suppressed and fine inspiratory rales are present. After a few hours or a day classical signs of consolidation appear. Pleural friction rub may be present. During resolution signs of consolidation are replaced by rales.

**B Laboratory Findings.** Sputum examination reveals numerous white cells, red cells and pneumococci. Application of the matching type of rabbit antiserum results in the capsule agglutinating reaction (Neufeld).

Leukocytosis with a WBC of 20,000-30,000/cu. mm. is the rule.

Blood cultures are positive in about 25% of cases.

**C X-ray Findings.** These are often absent at onset. A veil-like haziness appears after a few hours, then spreads and becomes more opaque until the full blown picture of consolidation is present. During resolution the opacity becomes patchy and may give the appearance of distinct radiolucent areas (pseudo cavitation).

### Treatment

Before beginning therapy obtain sputum and blood for culture in order to determine the exact bacterial invader. This is imperative if the infection is severe. Treatment with one of the specific agents listed below should be started pending the outcome of cultures.

Note: Therapy varies with the severity of the disease. Unfavorable prognostic signs include the following: Age over 45, presence of other disease (especially heart failure or cirrhosis), pregnancy, large number of pneumococci in the sputum, bacteremia, failure of leukocytosis, heavy proteinuria, shock and pulmonary edema. Patients with one unfavorable prognostic sign should be classified as severe, with 2 or more as very severe.

**A Specific Measures.** Penicillin is the drug of choice in pneumococcal infections. Chlorotetracycline, oxytetracycline, tetracycline, erythromycin, and chloramphenicol are also highly effective in most pneumococcal infections. The sulfonamide drugs are also effective, but the response to penicillin is usually more rapid and complications are less frequent when penicillin is used.

1. Mild to moderate cases - Penicillin or broad spectrum antibiotics may be used.

Continue until the patient has been afebrile for at least 72 hours and the WBC is normal. Give one of the following:

(1) Penicillin procaine in aqueous suspension or in oil, 300,000 units I.M. twice daily or 50-100 thousand units aqueous penicillin I.M. every 6 hours or 200,000 units orally every 4 hours. In general oral penicillin should be reserved for use after a favorable response to parenteral penicillin has been obtained.

(2) Chlorotetracycline (Aureomycin<sup>®</sup>), oxytetracycline (Terramycin<sup>®</sup>) or tetracycline 0.25 Gm. every 6 hours or chloramphenicol (Chloromycetin<sup>®</sup>) 0.5 Gm. every 6 hours, or erythromycin 0.3-0.5 Gm. every 6 hours.

(3) The sulfonamides may be used (see Chapter 20).

2. Moderate to severe cases - In severe cases give intermittent I.M. aqueous penicillin in doses of 100,000 units every 3 hours day and night or 1 million units of penicillin procaine I.M. every 12 hours. Continue penicillin therapy until the patient has been afebrile for 72 hours and the WBC is normal. One of the tetracyclines 0.5 Gm. every 6 hours or sulfonamides may be used in patients sensitive to penicillin.

3. Very severe cases -

(1) Patients with very severe pneumonia should be given massive penicillin therapy in an attempt to achieve a pneumococcal concentration of penicillin in infected areas as rapidly as possible. Combinations of penicillin and broad spectrum antibiotics or sulfonamides offer no advantages over penicillin alone. Give 1 million units of aqueous penicillin I.M. every 2 hours or continuous I.V. or I.M. drip 10-12 million units daily until a favorable clinical response occurs.

(2) Chlorotetracycline, oxytetracycline or tetracycline 0.5 Gm. I.V. every 12 hours or erythromycin or chloramphenicol, 0.5 Gm. every 6 hours until a favorable clinical response occurs.

(3) Sulfonamides - Give 5 Gm. (75 gr.) of sulfisoxazole (Gantrisin<sup>®</sup>), sodium sulfadiazine or sodium sulfamerazine, or a mixture of the sodium sulfadiazine and sodium sulfamerazine I.V. at once and follow with oral or I.V. maintenance as indicated. Maintain adequate alkalization of urine and fluid intake.

**B Evaluation of Therapy.** If there is no response to therapy in 24-36 hours, complete re-evaluation is indicated. The infection may be caused by an organism or strain which is resistant to the antimicrobial agent being used. If pneumococcal etiology is in doubt, broad-

spectrum antibiotics are usually preferable to penicillin. If pneumonia is spreading, treat as for very severe pneumonia and substitute one of the tetracyclines or chloramphenicol for the drug being given. Observe carefully for the development of complications, e.g., empyema (any pleural fluid collections must be aspirated promptly to detect empyema) lung abscess, endocarditis, and meningitis. Search for associated disease that may cause fever.

### C. General and Supportive Measures

1. Oxygen must be given to any patient with severe or moderately severe pneumonia, cyanosis, or marked dyspnea. It may be administered in several ways. The soft rubber facial mask of the BLB, OEM, or Bennett type is probably best. With these masks oxygen concentrations up to 95% may be easily maintained. Oxygen tents are most often used for patients in toxic delirium who would otherwise remove the mask, the tent has the disadvantage of maintaining oxygen concentrations of only 40-50%, and CO<sub>2</sub> may accumulate. Oxygen must be humidified to prevent drying of secretions.

2 Shock and pulmonary edema - The usual causes of death in pneumonia are shock and pulmonary edema. Treat shock as outlined on p 3. Clear the airway by means of tracheal suction, an endotracheal tube, or tracheostomy. Because anoxia may lead to shock and pulmonary edema in pneumonia, oxygen therapy, preferably with a positive pressure face mask, is of utmost importance.

3. Toxic delirium - The excitement and activity of the delirium which may occur in severe pneumonia must be controlled to prevent exhaustion and circulatory failure. Promazine (Sparine®) 50-100 mg. I.M. (or other phenothiazines in comparable doses) is the drug of choice for this purpose. Mild restlessness and sleeplessness may be treated with pentobarbital sodium, 0.1 Gm (1/2 gr) at bedtime, and phenobarbital, 15-30 mg (1/4-1/2 gr) t.i.d. during the day.

Paraldehyde is still a useful drug also. Give 8 ml. (2 dr.) orally stat., if there is no response in 30 minutes, repeat the dose until the patient is quiet. Then give 4-15 ml. (1-4 dr.) orally every 3-4 hours p.r.n. restlessness. If the patient is unable to swallow, give 4 ml. (1 dr.) I.M. at once, if there is no response in 30 minutes, repeat the dose until the patient is quiet. Then give 4-8 ml. (1-2 dr.) I.M. every 3-4 hours p.r.n. restlessness.

4. Fluids - Oral and parenteral fluid intake must be adequate to maintain a daily urine output of at least 1500 ml.

5. Diet - During the severe acute phase

patients usually have little desire for food. It is not necessary to encourage food intake during a short interval of anorexia. The patient who develops complications and is faced with a long convalescence should be placed on a high-protein, high-vitamin, high-caloric diet.

6. Cough - Remedies containing codeine should be given if cough interferes with rest and sleep. Give codeine phosphate, 15-30 mg. (1/4-1/2 gr) every 3-4 hours orally or subcut., or a liquid preparation such as elixir terpin hydrate with codeine, 1 tsp. every 3-4 hours p.r.n.

7 Pleuritic pain - For mild pain spray ethyl chloride over the area of greatest pain for about one minute, and then along the long axis of the body through the entire area of pain, so that a line of frost about one inch wide is formed. This gives relief for 1-10 hours in the great majority of patients. Codeine phosphate, 15-30 mg (1/4-1/2 gr), may be given as necessary for pain. For severe pain give procaine hydrochloride solution, 1/2-1%, subcut., in a series of injections passing through the area of greatest pain and 5 cm (2 in.) higher and lower. For very severe pain use meperidine (Demerol®), 50-100 mg, or morphine sulfate, 10-15 mg (1/6-1/4 gr).

8 Abdominal distention usually due to air swallowing in severe dyspnea, is a frequent problem in patients with pneumonia. Oxygen in high concentrations (90-100%) is useful because it is rapidly absorbed from the intestines. Neostigmine methylsulfate, 1/2000, 1 ml subcut., and insertion of a rectal tube will usually produce rapid initial decompression. Gastric dilatation can be relieved by suction through a nasal tube passed into the stomach.

9. Congestive failure - (Distinguish from shock and pulmonary edema.) In elderly patients or patients with preexisting heart disease, congestive failure may be precipitated by pneumonia. Rapid digitalization is indicated (see p 231).

10. Cardiac arrhythmias - Extrasystoles usually require no treatment. If atrial fibrillation or flutter develops, rapid failure may be precipitated. Rapid digitalization is usually indicated in these cases (see p 231).

11. Alkalinization of urine - Patients taking sulfadiazine should be given sufficient alkalinizing drugs to maintain the pH of urine above 7. Potassium bicarbonate should be used in patients with actual or potential heart failure, care being exercised to avoid potassium toxicity.

### Complications.

The following list of incidences is modified after Collen. Sterile pleural effusion

(. 5%) empyema lung abscess pericarditis (0.3% each) endocarditis meningitis (0.1% each) All pleural effusions associated with pneumonia should be aspirated promptly so that empyema can be detected and treated early (see p. 157)

### Prognosis

Mortality since the advent of penicillin has dropped from about 30% (untreated cases) to 5% or less. In untreated cases resolution by crisis occurs in 7-10 days unless the patient dies.

- Finland M. Treatment of pneumonia and other serious infections. Shattuck Lecture. New England J. Med. 263:207-21. 1960.  
 Kingston J. R. & others. Eaton agent pneumonia. J. A. M. A. 176:118-23. 1961.  
 Reiman H. A. Pneumonia. Thomas. 1954.

## UNCOMMON SPECIFIC BACTERIAL PNEUMONIAS

Pneumonias due to organisms other than the pneumococcus constitute only a small percentage (less than 5-10%) of pneumonias due to a single bacterial organism. They have in common the features of patchy infiltrations on x-ray and lack of extensive areas of consolidation such as are characteristic of pneumococcal pneumonia. Sputum studies reveal a single predominant organism. Pneumonias of this type are not readily distinguishable from each other on clinical grounds.

Isolation of organisms from sputum and blood culture is especially important in this group to allow selection of an appropriate therapeutic agent. Examination of a stained smear of sputum is always indicated.

### Streptococcal Pneumonia

Streptococcal pneumonia is usually secondary to a viral pulmonary infection (e.g., viral pneumonia, influenza or measles). Most cases are due to beta-hemolytic streptococci. Onset is most often gradual but may be sudden with severe irritation, marked dyspnea and cough with bloody or mucopurulent sputum. In many cases pleural effusion occurs early and may progress to empyema. Physical findings vary with severity; there may be only scattered dullness and moist rales. In severe cases pleural effusion obscures the pulmonary signs. The throat is usually reddened and has some exudate.

Penicillin is the drug of choice. The dosage is similar to that for pneumococcal pneumonia. Recovery is the rule.

### Staphylococcal Pneumonia.

Staphylococcal pneumonia is increasing in incidence, especially in postsurgical or debilitated patients or secondary to influenza, measles or other viral infections. The onset may be insidious or fulminant. Cough and dyspnea are common. Multiple lung abscesses and empyema occur frequently. Patchy consolidation and diffuse rales are often found.

Sensitivity tests should be performed to determine the appropriate antibacterial agent. Pending the results of tests, all of the following should be given: I.M. every 6 hours: erythromycin (Erythrocin®) 0.5 Gm, novobiocin sodium (Cathomycin®) 0.5 Gm, chloramphenicol (Chloromycetin®) 0.5 Gm, bacitracin 20,000 units and penicillin procaine G 2.5 million units. Therapy should be prolonged (at least 2 weeks). Alternatively, methicillin (Staphicillin®) 10-12 Gm/day may be given.

The prognosis depends largely upon the susceptibility of the organism to antibiotics. The mortality rate is very high with resistant organisms.

### Friedländer's Pneumonia

Pneumonia due to *Klebsiella pneumoniae* is often associated with chronic debilitating disease. The onset is usually sudden with chills, fever, dyspnea, cyanosis, cough and marked toxicity. The disease progresses rapidly to a fatal termination unless the patient responds well to early intensive therapy as outlined below. There is a tendency to necrosis and abscess formation in the subacute or chronic forms.

Physical findings are variable. The only signs of extensive involvement may be dullness and diminished breath sounds. The sputum is red, mucoid and tenacious, giving a currant jelly appearance. Leukopenia or leukocytosis may occur or the WBC may be normal.

Friedländer's pneumonia must be treated intensively. Give streptomycin sulfate 1 Gm I.M. every 6 hours until a favorable response is obtained and then 0.5 Gm every 6 hours until the patient has been afebrile for 3 days. In addition to streptomycin therapy, give one of the following: a tetracycline drug (I.M. or I.V.) or chloramphenicol (Chloromycetin®) 0.5 Gm every 6 hours I.M. or sulfisoxazole (Gantisin®) 1 Gm every 6 hours I.M. or I.V. Continue antibiotic therapy for 2-3 weeks. General measures are as for pneumococcal pneumonia.

The mortality rate is high in acute Friedländer's pneumonia: 80% in untreated cases and 40% with treatment.

**Hemophilus influenzae Pneumonia.**

*Hemophilus influenzae pneumonia* is rare. The disease usually begins suddenly and progresses rapidly. The outstanding features are severe involvement of the bronchi and bronchioles, leading to bronchiectasis and hemorrhagic edema of lungs. Patients are extremely toxic. X-ray shows patchy consolidation of the lung fields, and the sputum is bloody.

Combined streptomycin and sulfonamide therapy is the treatment of choice. Give streptomycin sulfate, 0.5-1 Gm. every 6 hours I.M., and sulfonamides as for very severe pneumococcal pneumonia. An alternative is to give tetracyclines (I.M. or I.V.) or chloramphenicol (Chloromycetin®), 0.5 Gm. every 6 hours, plus sulfonamides as for severe pneumococcal pneumonia.

Continue antibacterial treatment for 7-10 days after the temperature has returned to normal. General measures are as for pneumococcal pneumonia.

With appropriate therapy, recovery is the rule.

See references under *Pneumococcal Pneumonia*.

**"MIXED TYPE" BACTERIAL PNEUMONIAS**  
(Hypostatic Pneumonia, "Terminal"  
Pneumonia, Bronchial Pneumonia)

**Essentials of Diagnosis.**

- Variable onset of fever, cough, dyspnea, expectoration.
- Symptoms and signs often masked by primary (debilitating) disease.
- Greenish-yellow sputum (purulent) with mixed flora.
- Leukocytosis (often absent in aged and debilitated)
- Patchy infiltration on chest x-ray.

Differentiate from tuberculosis, carcinoma, and other specific mycotic, bacterial, and viral pulmonary infections (to any of which it may also be secondary)

**General Considerations.**

Mixed bacterial pneumonias include those in which culture and smear reveal several organisms no one of which can clearly be identified as the etiologic agent. Many "terminal" pneumonias in hospitalized patients are due to staphylococci. These pneumonias usually appear as complications of surgery or other trauma, various chronic illnesses (cardiac failure,

advanced carcinoma, uremia), and certain acute illnesses (e.g., measles, influenza). They are common complications of chronic pulmonary diseases such as bronchiectasis and emphysema. Old people are most commonly affected.

The following findings in a debilitated, chronically ill, or aged person suggest a complicating pneumonia (1) worsening of cough, dyspnea, cyanosis, (2) low-grade, irregular fever, (3) purulent sputum, and (4) patchy basal densities on a chest film (apart from previously noted densities caused by a primary underlying disease, if any)

**Clinical Findings**

**A Symptoms and Signs** The onset is usually insidious with low-grade fever, cough, expectoration, and dyspnea which may become marked and lead to cyanosis. The physical findings are extremely variable, and may not be impressive against a background of chronic cardiac or pulmonary disease. Those signs listed under other bacterial pneumonias may also be present with this type.

**B Laboratory Findings** The appearance of a greenish or yellowish (purulent) sputum should suggest a complicating pneumonia. Smears and cultures reveal a mixed flora. Predominant types should be noted as a guide to therapy. Leukocytosis is often absent in the aged and debilitated patient.

**C X-ray Findings** X-ray shows patchy, irregular infiltrations, most commonly posterior and basal (in bedridden patients). Abscess formation may be observed. Careful interpretation is necessary in order to avoid confusion with shadows due to preexisting heart or lung disease.

**Treatment.**

Where no specific etiologic microorganisms are present in the sputum, broad-spectrum antibiotics should be used. Give tetracycline, 0.25 Gm. every 6 hours orally, or 0.1 Gm. every 8 hours I.M. If staphylococci are present in the sputum in large numbers, treat as for staphylococcal pneumonia.

**Prognosis.**

The prognosis depends upon the presence of underlying pulmonary disease and varies with the predominating organism.

See references under *Pneumococcal Pneumonia*.

## PRIMARY ATYPICAL PNEUMONIA

### Essentials of Diagnosis

- Increasing cough and fever with scanty sputum
- S gns frequently sparse rales only
- X ray evidence of marked infiltration
- Normal to low WBC cold agglutinins in convalescent phase

Differentiate from other pneumonias tuberculosis and neoplastic lung diseases

### General Considerations

Primary atypical pneumonia is presumably of viral origin. Many viruses may produce this syndrome including adenovirus, Eaton agent (pleuropneumonia) and influenza virus. The incubation period is 7-21 (usually 12) days and the course is benign (about 2 weeks). Transmission is by droplet infection from the nose and mouth of an infected person. This is the most common type of pneumonia encountered in otherwise healthy young adults.

### Clinical Findings

**A Symptoms and Signs** The clinical picture varies widely both in the spontaneous and experimentally induced forms. Symptoms may be mild as in the common cold, grippe or flu, hence the likelihood that many diseases previously diagnosed as upper respiratory infection were in fact pneumonias. Occasional severe cases occur which may be fatal.

The disease often begins as a mild upper respiratory tract infection proceeding to a dry cough which grows worse, increasing fever, hoarseness, headache and generalized aching. Extreme fatigue is common.

Physical findings are frequently sparse and sometimes completely absent in the face of a surprising degree of infiltration as seen on x ray. Rales are usually heard. Diminished breath sounds over the involved areas may be noted in early cases.

**B Laboratory Findings** The sputum is scanty, rarely pink tinged. The smear shows a striking lack of bacteria and yields only the usual flora of the mouth on culture. The WBC may be normal or may show mild to severe leukopenia. Mild leukocytosis may appear later in the course of the disease. Abnormal lymphocytes (virocytes) resembling those of infectious mononucleosis occasionally are seen.

Autohemagglutinins for human type O erythrocytes (cold agglutinins) appear in the convalescent phase (seldom before the second week) in about 50% of cases. To be significant, a rise in titer must be  $> 1:10$  during the second week.

Agglutinins for streptococcus MG also have been reported in the convalescent phase in 50% of patients.

**C X ray Findings** Linear infiltrations tend to appear first at hilar areas, extending later into the middle and basal portions of both lungs. The initial appearance of these changes may be delayed and clearing on x ray usually occurs within 3 weeks. There is considerable variation in the x ray pattern and no configuration is diagnostic. Upper lobe lesions in particular lead to diagnostic difficulties.

**Complications** Sterile pleural effusions occur in about 5% of cases. Atelectasis, pneumothorax, pericarditis, myocarditis, secondary bacterial pneumonia, and acute hemolytic anemia may occur. Bronchiectasis also has been seen as a late complication.

### Treatment

Give one of the tetracyclines 0.25-0.5 Gm every 6 hours orally. IV therapy may be necessary in severe cases or if the patient is vomiting and may be combined with oral therapy in resistant cases. Give 0.5 Gm every 12 hours. Treatment is effective only in pneumonias caused by the Eaton agent.

General measures are as for pneumococcal pneumonia (see p. 135).

### Prognosis

Mortality in untreated cases is low. Fever usually disappears by the tenth day, although x ray abnormalities persist for longer periods.

See references under Pneumococcal Pneumonia.

## LIPOID PNEUMONIA

This disease is an aspiration pneumonia associated with the use of oily medications. Fibrosis and the presence of macrophages containing oil droplets are the histologic features.

Symptoms and signs vary widely at times resembling those of acute pneumonia (fever, productive cough) or chronic lung disease (weight loss, night sweats). There may be no symptoms but striking x ray densities. Patients must be carefully questioned about the use of mineral oil, oily nose drops, or ointments used.



in the nose. Physical signs vary accordingly and are not diagnostic. Peribronchial infiltrations, diffuse lobar densities, scattered discrete densities, and even central cavitation have all been described on x-ray. Leukocytosis may occur with acute symptoms. Sputum or bronchial aspirate may reveal oil droplets. Exploratory thoracotomy may be required in view of the many diagnostic possibilities.

Treatment is nonspecific and symptomatic. Use of the oil-containing preparation should be discontinued. When this is done, further progression of the disease usually does not occur and the prognosis is good. Large solitary masses may require resection.

Hewlett, T., & others: Lipoid pneumonia.

Am. Pract. & Digest, Treat. 12:85, 1961

Rubin, E.H.: Thoracic Disease, Emphasizing Cardiopulmonary Relationships. Saunders, 1961.

### PNEUMONIAS DUE TO SPECIFIC VIRUSES & RICKETTSIAE

The important specific viral and rickettsial infections which may produce pneumonia include influenza, psittacosis (ornithosis), Q fever, Rocky Mountain spotted fever, and typhus. The exanthematous viral diseases (rubella, varicella, variola, and vaccinia) are all thought to give rise occasionally to specific pneumonias.

These pneumonias are indistinguishable from primary atypical pneumonia on the basis of pulmonary physical and x-ray findings. Diagnosis depends upon recognition of the specific systemic disease by extrapulmonary features (e.g., rash), a history of exposure to a specific virus (e.g., parrots), epidemiologic information, and demonstration of a significant rise in specific antibody titers.

The treatment of viral pneumonia is symptomatic. Treat rickettsial pneumonias as outlined in the discussion of rickettsioses.

See references under Pneumococcal Pneumonia.

### PULMONARY INFILTRATION WITH EOSINOPHILIA (PIE Syndrome)

This relatively uncommon syndrome is characterized by migratory multiple pulmonary infiltrates, eosinophilia (up to 80%) in the pe-

ripheral blood, and variable symptomatology. It is believed to represent an allergic response to a number of diseases, including parasitic infections (*Entamoeba histolytica*, *Trichuris*, *Fasciola hepatica*), bacterial and mycotic infections (tuberculosis, brucellosis, coccidioidomycosis), and certain of the "collagen" diseases.

Treatment and prognosis depend upon the underlying disease.

Reeder, W.H., & B.E. Goodrich: Pulmonary infiltration with eosinophilia (PIE syndrome). *Ann Int Med.* 36:1217-40, 1952.

## PULMONARY TUBERCULOSIS

### Essentials of Diagnosis

- Presenting signs and symptoms are usually minimal malaise, lassitude, easy fatigability, anorexia, mild weight loss, afternoon temperature rise, cough, apical rales, hemoptysis (10-20%).
- Recent reversal of tuberculin skin test from negative to positive.
- Apical or subapical infiltrates, often with cavities
- *Mycobacterium tuberculosis* in sputum or in gastric or tracheal washings.

Pulmonary tuberculosis must be considered whenever apical lesions are found. Unexplained pleural effusion in an adolescent or young adult must be regarded as tuberculosis until proved otherwise. Since tuberculosis is a great imitator, it must be differentiated from other pulmonary diseases such as pneumonia. Infiltrations confined to the anterior portions of the lungs or to the lower lobes are usually not due to tuberculosis.

### General Considerations.

Pulmonary tuberculosis is a specific pulmonary infection caused by the acid-fast organism, *Mycobacterium tuberculosis*, and characterized by the formation of tubercles in involved tissue. Negroes, American Indians, and Orientals are especially susceptible to progressive, extensive disease. The "primary" infection in children is usually a self-limited disease which escapes clinical detection. The progressive "reinfection" type is characteristically first noted in young adults (rarely before puberty). Malnutrition, diabetes, and chronic steroid administration adversely affect the course of the disease.

### Clinical Findings

**A Symptoms and Signs** Symptoms are fewer and milder than the extent of the disease (as seen on chest films) would suggest. In general, if systemic and pulmonary symptoms are present and pulmonary lesions can be seen on x-ray, the disease may be regarded as active. However, lack of symptoms does not rule out activity.

Symptoms are usually absent in primary (childhood) infection. Minimal reinfection tuberculosis is seldom diagnosed on the basis of symptoms.

Malaise, lassitude, easy fatigability, and anorexia and mild weight loss are the symptoms most often noted at diagnosis in the childhood and adult types. Low grade afternoon fever may be present. High fever usually accompanies the disseminated and pneumonic forms of the disease.

Cough may be productive or nonproductive. Hemoptysis is the presenting feature in 10-20% of cases. Wheezing and marked cough are pronounced with bronchial tuberculosis. A history of a cold that hangs on or of a cigarette cough is not infrequent.

Pleural involvement may produce pleuritic pain, vague chest discomfort, or dyspnea.

Tuberculous patients occasionally present with such widely divergent symptoms as those due to cystitis, epididymitis, osteomyelitis of the spine, meningitis, and hypoadrenocorticism. Search for and evaluation of activity of coexisting pulmonary lesions must not be neglected. Absence of physical signs is the most noteworthy feature of pulmonary tuberculosis. Pulmonary lesions presenting with marked physical signs are not often due to tuberculosis.

Rales in the upper lung fields are the most common signs. These are apt to be heard in the infraclavicular, axillary, and interscapular areas and are best elicited after a light cough.

Advanced disease may lead to retraction of the chest wall, depression of supraclavicular fossae, wheezes and rales of every description, and patches of consolidation. Signs of cavitation are unreliable.

Lower lobe pulmonary signs speak against a diagnosis of tuberculosis.

Pleural effusion without an obvious explanation, especially in adolescents and young adults, is considered to be due to tuberculosis until proved otherwise.

Laryngeal lesions may be visualized by mirror examination.

### B Laboratory Findings

1 The tuberculin skin test. This test is based on skin hypersensitivity to a specific

bacterial protein obtained from culture media. Tuberculin may be administered intracutaneously (Mantoux) by patch test (Vollmer) by scarification (Pirquet) and by various newer methods. The intracutaneous method employing purified protein derivative (PPD) is still considered the most reliable.

(1) A positive reaction indicates past or present infection. The skin test becomes positive 2-8 weeks after infection with the tubercle bacillus. The incidence of positive reactions varies with populations but occurs in a majority of adults in some urban areas.

(2) A negative reaction for all practical purposes rules out tuberculous etiology of pulmonary disease. Anergy (disappearance or marked decrease of the tuberculin reaction) is a rare phenomenon of overwhelming tuberculosis, exanthematous diseases, and sarcoidosis. The possibility of defective testing material must also be considered.

(3) A conversion or negative reaction which becomes positive during observation means recent infection and is an important finding, especially in children and people with greater than normal exposure (e.g., nurses, physicians, hospital workers).

2 Bacteriologic studies. Recovery of the tubercle bacillus from sputum or gastric washings is the only incontrovertible diagnostic finding.

(1) Sputum. Direct smears are positive when the bacterial count is high. Concentrated 24-hour specimens are done if direct smears are negative. Positive smears should always be confirmed by culture, although treatment is usually started before culture reports are completed.

Culture is more sensitive than smears but the time required for growth of organisms (4-6 weeks) is a disadvantage. Certain atypical acid-fast organisms may cause confusion. If positive cultures are not entirely typical or are inconsistent with clinical findings, guinea pig inoculation is essential. Typical lesions are found in the necropsied animal.

(2) Gastric washings. Stained smears of gastric washings are of no value because of the occurrence of nontuberculous acid-fast organisms. Cultures and guinea pig inoculations are especially useful for patients who swallow their sputum (e.g., children). Recovery of the organism occurs in 20-30% of cases of active primary tuberculosis (where sputum is frequently absent).

3 Enlarged lymph nodes in supraclavicular or cervical areas should be sought for carefully since they may allow a simple direct (biopsy) diagnosis of underlying pulmonary disease.

**C X-ray Findings.** Chest films disclose lesions in almost all cases and are far more helpful than any other procedure in the discovery of pulmonary tuberculosis. Failures occur where lesions are hidden behind ribs, cardiovascular structures, and the diaphragm. A single film does not establish or rule out activity. Although many features may suggest the likelihood of tuberculous etiology, there is no pathognomonic x-ray pattern.

Hilar lymph node enlargement associated with a small parenchymal lesion which heals with calcification is the usual picture of primary infection. Many "primaries" (proved by change of tuberculin skin test from negative to positive) do not present x-ray abnormalities. Very large nodes are unusual in adults, where "primary" infection cannot be distinguished from "reinfection" on x-ray grounds.

Apical and subapical infiltrations are the usual presenting x-ray features of "adult" (reinfection) tuberculosis. Lordotic views may be required to reveal such lesions where uncertainty exists in the posteroanterior projection.

Cavitation is presumptive evidence of tuberculous activity. Tomograms are occasionally necessary for the demonstration of cavities.

Fibrotic disease, with dense, well-delineated strands, may dominate the picture. The physician should not be deluded into considering such lesions inactive ("scars").

Solitary nodules, miliary lesions, and lobar consolidation (acute caseous pneumonia) present difficult problems in differential diagnosis.

Tuberculous pleural effusion has no characteristic x-ray appearance that differentiates it from other effusions.

Basal tuberculosis is seldom seen in the absence of upper lobe lesions (1-1½% of cases).

Bronchial tuberculosis may lead to obstruction and bronchiectasis, with corresponding x-ray findings.

Serial films are often crucial in the establishment of activity and are indispensable in the selection and evaluation of therapy.

### Differential Diagnosis.

Tuberculosis can mimic nearly any pulmonary disease. Important diseases to be considered are bacterial and viral pneumonias, lung abscess, pulmonary mycoses, bronchogenic carcinoma, sarcoidosis, and pneumoconioses.

Recovery of the tubercle bacillus by culture or guinea pig inoculation establishes the diagnosis of tuberculosis.

A negative tuberculin skin test, with few exceptions, excludes tuberculosis.

If carcinoma is suspected and cannot be promptly excluded, early tissue diagnosis by thoracotomy may be indicated without waiting for positive cultures.

### Prevention

**A Isolation Precautions.** Persons in contact with patients who have active tuberculosis must protect themselves by wearing masks and gowns and washing their hands thoroughly after each contact with a patient. The patient must be instructed in how to cough so as not to infect others and taught to dispose of his sputum properly. Hospital personnel in contact with tuberculosis patients should have routine skin tests (in nonreactors) or chest x-rays at least twice a year.

**B Examination of Contacts.** Close contacts must be examined by skin test and chest x-ray when an active case is discovered and again in 2-3 months. Tuberculin converters and young children with positive skin tests should be treated with isoniazid (see below). Other tuberculin-positive contacts should have chest x-rays every 6 months for 2 years and then annually.

**C BCG Vaccination.** Although it is generally agreed that BCG vaccination offers some protection to tuberculin-negative persons, several factors limit its usefulness. In most parts of the world the risk of developing tuberculosis is slight among tuberculin-negative persons. Converting tuberculin-negative people to positive reactors by vaccination deprives the clinician of an important tuberculosis control measure, i.e., the discovery of early infection by skin testing, and treatment of converters with isoniazid. In addition, the difficulty of obtaining and administering a potent BCG vaccine makes it impractical for occasional use. For these reasons, BCG vaccination is recommended only where exposure to tuberculosis is great and the usual tuberculosis control measures are not operative.

**D Treatment of Tuberculin Reactors (Without Other Evidence of Disease).** Most authorities now recommend the treatment of anyone known to have been infected with tuberculosis within the preceding year. Children up to age 3 with a positive tuberculin reaction should routinely receive a course of drug treatment. Adolescents with strongly positive tuberculin tests (in excess of 20 mm. induration) should also be treated. This "protective" treatment consists of isoniazid, 5 mg/Kg/day for at least one year. Activities need not be

restricted Pretreatment x rays must show no evidence of tuberculosis X rays should be repeated in 3 months and 9 months and annually thereafter

### Treatment

**A Rest** Bed rest and mental relaxation in cheerful comfortable surroundings either at home or in a sanatorium should be instituted whenever an active lesion exists or is probable This is still an important measure in the therapy of pulmonary tuberculosis although the duration of the rest period required has been greatly reduced by the antituberculosis drugs When symptoms are absent or disappear complete ambulation and light diversional activities may be permitted

Most authorities recommend sanatorium care initially for patients with active pulmonary tuberculosis For patients with early disease few symptoms and adequate homes 6-8 weeks in the hospital are usually sufficient to establish a good treatment program and eliminate the risk of contagion Patients with advanced disease are usually ready for home care in 4-6 months Prolonged hospitalization may be required when (1) very extensive disease is present (2) the disease fails to respond to adequate treatment or (3) the patient's home is not suitable for home care

Some patients for emotional social or economic reasons are best treated only at home The safety of other members of the family undisturbed rest periods and the proper administration of medicines must be provided for and medical care must be available

**B Drug Therapy** Drug treatment is the most important single measure in the management of tuberculosis although it must be combined with rest and where indicated surgical treatment Drug therapy is indicated in all cases of active disease and is most effective when used in conjunction with a well regulated program of bed rest and surgery when indicated (see below) In general the return to limited physical activity is permitted sooner with drug therapy and gradual ambulation may be started as soon as clinical improvement is well established

The present recommendation is for prolonged administration of combinations of the drugs listed below (except viomycin and pyrazinamide) Many patients seem to benefit from prolonged treatment even after moderate resistance of the organisms to the drugs has been shown by sensitivity tests Most authorities advise a minimum of 12 months of drug treatment after the inactive status has been attained (National Tuberculosis Association)

The principal drugs now used in the treatment of pulmonary tuberculosis are isoniazid (INH) streptomycin and aminosalicylic acid (PAS) The simultaneous use of these 3 drugs is probably justifiable for gravely ill patients but in the more chronic forms of pulmonary tuberculosis no definite advantage has been shown In general it is probably wise to withhold streptomycin for possible later use (e.g. with surgery)

**1 Isoniazid (INH)** This is the most effective drug currently available However when used alone its effectiveness is decreased by the early development of bacterial resistance It should be used with at least one of the other drugs listed below

Isoniazid is indicated for any active tuberculous lesion including primary tuberculosis in children It is of particular value in millary tuberculosis tuberculous meningitis streptomycin resistant tuberculosis and streptomycin intolerance Toxic reactions are infrequent in the usual dose of 5 mg/Kg/day They include dermatitis and febrile reactions With larger doses peripheral neuropathy and rarely CNS irritability may occur There is evidence that the latter are related to pyridoxine depletion Supplementary doses of pyridoxine (25-50 mg/day) should be given

**2 Streptomycin sulfate** The indications for this drug are the same as for isoniazid except that it is less effective than isoniazid in advanced tuberculosis Like isoniazid it is less effective when used alone and whenever possible should be given in combination with at least one of the other drugs

Streptomycin and dihydrostreptomycin are essentially alike in therapeutic effect However since the toxicity of dihydrostreptomycin for the eighth nerve (deafness) is more serious than that of streptomycin (vertigo) the latter should be used

Toxic reactions to streptomycin are few when the drug is given twice weekly This regimen produces a therapeutic effect comparable to that of other streptomycin schedules (except in the more serious forms of the disease where daily dosage may be necessary) Generalized dermatitis occasionally occurs in which case the drug must be discontinued Perioral numbness often appears shortly after injection and may last for several hours By itself it can be ignored

**3 Aminosalicylic acid or its calcium or sodium salt** This drug has a low level of antituberculous activity but when used with streptomycin or isoniazid it delays the emergence of resistant organisms Toxic reactions include nausea vomiting and diarrhea a febrile reaction and occasionally generalized der-

## Antituberculosis Drugs

Drug	Adult Dose	Remarks
oniazid (INH)	5-10 mg./Kg./day*	Only indication for using these drugs singly is hypersensitivity of the patient or known resistance of bacilli to other drugs.
reptomycin	1 Gm. daily or twice weekly.	
minosalicic acid (PAS)	4-5 Gm. t.i.d., p.c	Any 2 of these 3 drugs may be used (except in severe disease, where all 3 are indicated) Use INH whenever possible in severe disease use streptomycin daily until improvement is established (then twice weekly) and INH, 10 mg./Kg./day
Combined Therapy Streptomycin and Aminosalicic acid and isoniazid	1 Gm./day or 1 Gm. twice weekly.	
	4-5 Gm. t.i.d., p.c. (with either of above schedules)	
	5-10 mg./Kg./day* (with either of above schedules)	

\*divided doses. When 10 mg./Kg./day is used, pyridoxine, 25-50 mg (3/8-3/4 gr)/day should be given.

dermatitis. The gastrointestinal symptoms may sometimes be overcome by using a different preparation or by stopping the drug for several days and then resuming it in small doses, gradually increasing to the regular dose in 2-3 weeks. When fever or dermatitis due to PAS toxicity occurs, the drug usually must be stopped.

4. Viomycin sulfate (Vinactane®, Viocin®), less effective and more toxic drug than streptomycin, has limited usefulness where chemotherapy is needed and the above-mentioned drugs cannot be used (hypersensitivity, resistant organisms). The usual dose is 2 Gm. 1 M. orally or twice weekly for up to 6 weeks.

5. Pyrazinamides (pyrazinoic acid amide, PZA), a drug which occasionally produces severe toxic hepatitis, can be used alone or with isoniazid for 1-3 months when resistance or hypersensitivity prevents use of the other drugs. Observe carefully for symptoms and laboratory evidence of liver dysfunction, and stop the drug promptly if any abnormality appears. The usual adult dose is 0.75 Gm. orally twice daily.

6. Cycloserine (Seromycin®) has limited antituberculosis activity but is useful when bacterial resistance to the major drugs is present, especially in connection with resectional surgery. The usual adult dose is 250 mg. b.i.d. orally. It may cause CNS irritability. When larger doses are used, pyridoxine hydrochloride, 50 mg./day, and diphenylhydantoin (Dilantin®), 100 mg. (1 1/2 gr.)/day, should be given.

C. Collapse Therapy: Collapse therapy is little used at present. Pneumoperitoneum may be helpful in the presence of persistent activity with cavitation when surgery is not possible.

## D. Surgery:

1. Pulmonary resection has gained increasing popularity in the treatment of pulmo-

nary tuberculosis in recent years, although only about 5-10% of patients now being treated in tuberculosis hospitals require major surgery. Pulmonary resection is indicated in any of the following circumstances (1) When there is a localized nodule, especially if the diagnosis is in doubt (2) For bronchiectasis causing persistent activity. (3) For bronchial stenosis. (4) For old thoracoplasty failures. (Some of these can be successfully treated by resection.) (5) For any localized chronic focus which has not become "inactive" (National Tuberculosis Association Diagnostic Standards, 1961) after 9-12 months of adequate nonsurgical therapy.

2 Thoracoplasty - The indications for thoracoplasty are decreasing, this procedure still has a place, however, in the following circumstances (1) For chronic cavity lesions when resection is not feasible and the lesser procedure can be tolerated (2) In certain cases where later resection is contemplated and it is felt that thoracoplasty will improve the patient's general condition (3) To reduce the pleural "dead space" after a large pulmonary resection and thus minimize overdistention of remaining lung tissue. (4) To close chronic empyema spaces.

E. Diet The diet should be adequate in calories and high in proteins and vitamins. One should attempt to keep the tuberculosis patient's weight above normal. No special diets have been shown to be of benefit.

F. Climate There is little evidence that climate is of any significance in the management of tuberculosis. The availability of good medical care is far more important. Excessive exposure of large skin areas to the sun should be avoided. Patients with tuberculosis should avoid exposure to industrial smoke and dust if possible.

**G Symptomatic Treatment** The patient should be reassured that his symptoms will disappear as the illness is brought under control

**1 Cough** In general cough in tuberculosis should not be suppressed with drugs. Nonproductive cough can usually be controlled by the patient. Productive cough should be encouraged and the patient told how to cough properly (i.e. without a violent inspiratory phase the actual cough should be without effort). If it becomes necessary to suppress exhausting cough give codeine phosphate 8-15 mg ( $\frac{1}{2}$  to  $\frac{3}{4}$  gr.) orally or benzonatate (Tessalon<sup>®</sup>) 100 mg every 4-6 hours as necessary may be helpful. Intermittent inhalation of 5-10% CO<sub>2</sub> with oxygen will diminish cough. Patients with large cavities who produce copious sputum may be helped by postural drainage. When secondary infection is present penicillin or broad spectrum antibiotics may be indicated.

**2 Night sweats** Avoid excessive bed clothing

**3 Hemorrhage** The chief danger of hemorrhage in tuberculosis is not sudden death but aspiration of the infected blood and spread of the disease to other parts of the lungs. Therefore use cough inhibitors carefully in the treatment of hemorrhage and do not give morphine.

Antishock therapy (see p. 3) should be instituted if bleeding is severe and shock is imminent. Reassurance is most important in allaying apprehension. Phenobarbital sodium 50-120 mg (1-2 gr.) subcut may be of value in quieting this apprehensive patient.

If severe bleeding continues emergency collapse therapy may be necessary. However it involves the danger of permitting spread of the disease.

Continued severe bleeding can sometimes be controlled with posterior pituitary injection, 1 ml (10 I.U.) slowly I.V. in 10 ml of normal saline.

**Absolute bed rest** is essential. The value of positioning is controversial but complete immobilization is unwise. Moving from time to time helps bring up secretions. Instruct the patient in the proper method of coughing (see above).

**H Response to Treatment** A favorable symptomatic response to treatment is usually reported within 2-3 weeks. Improvement can usually be observed on x-rays within 4 weeks and positive sputum usually becomes negative within 3 months. Repeat x-ray examination and sputum tests preferably cultures should be done at monthly intervals during the first few months of treatment. When improvement

is established the interval between x-rays can be lengthened. When sputum has been negative on 3 consecutive cultures and surgery is not indicated a rapid return to normal activities can be permitted. If there is no x-ray improvement or sputum conversion within 4 months the treatment program should be reevaluated. Tuberculosis is considered inactive when the following criteria (National Tuberculosis Association Diagnostic Standards) have been satisfied for at least 6 months: (1) No symptoms (2) x-ray appearance stable without evidence of cavitation and (3) sputum (or gastric or bronchial washings) negative for tubercle bacilli by culture.

### Prognosis

Very few people die of pulmonary tuberculosis when modern treatment methods are used before the disease reaches a very advanced stage. Most patients including those with advanced disease can be restored to a normal state of health within 12 months.

When the disease has been inactive for 2 years after the cessation of adequate treatment the danger of relapse is estimated to be less than 10%. However life long surveillance of all treated tuberculosis patients (and persons suspected of having active disease) is still strongly recommended.

Hinshaw H.C. & L.H. Garland Diseases of the Chest Chapters 27-32 Saunders 1956

Interim Report by Committee on Therapy Drug treatment of pulmonary tuberculosis Am Rev Resp Dis 81:438-40, 1960

Kass I. & others The residual lesion in pulmonary tuberculosis requiring surgery a review of 100 sputum negative patients consecutively operated on New England J Med 352:315-20, 1955

Lambert H.P. Chemoprophylaxis of tuberculosis review Am Rev Resp Dis 80:648-58, 1959

National Tuberculosis Association Diagnostic Standards and Classification of Tuberculosis 11th ed 1961

Pinner M. Pulmonary Tuberculosis in the Adult Its Fundamental Aspects 2nd ed Thomas 1951

## LUNG ABSCESS

### Essentials of Diagnosis.

- Development of pulmonary symptoms about 2 weeks after possible aspiration, bronchial obstruction, or previous pneumonia
- Septic fever and sweats, periodic sudden expectoration of large amounts of purulent, foul-smelling or "musty" sputum Hemoptysis may occur
- X-ray density with central radiolucency and fluid level.

Differentiate from other causes of pulmonary cavitation Friedländer's pneumonia, bronchogenic carcinoma, mycotic infections, and tuberculosis.

### General Considerations.

Lung abscess is an inflammatory lesion which has caused necrosis of lung tissue. It is characterized by the onset of pulmonary symptoms 10-14 days after clinical disruption of bronchopulmonary function or alteration of bronchopulmonary structure by any of the following means: (1) Aspiration of infected material (e.g., during oral surgery) (2) Suppression of cough reflex (e.g., in coma or with drugs) (3) Bronchial obstruction (e.g., post-operative atelectasis, foreign bodies, neoplasms). (4) Pneumonias, especially certain bacterial types. (5) Ischemia (e.g., following pulmonary infarction). (6) Septicemia (especially staphylococcal). Infection with pyogenic or anaerobic bacteria in any of these situations causes lung abscess. The usual location is the superior segment of the lower lobe or the lower portion of the upper lobe of the right lung. *Pleuritis and at times rupture into the pleural space, with bronchopleural fistula (empyema, pyopneumothorax) may occur.*

If inadequately treated, lung abscess usually becomes chronic.

### Clinical Findings.

**A Symptoms and Signs** Onset may be abrupt or gradual. Symptoms include fever (septic type) sweats, cough, and chest pain. Cough is often nonproductive at onset. Periodic sudden expectoration of large amounts of purulent, foul-smelling sputum followed by a remission of systemic symptoms is characteristic of lung abscess. Hemoptysis is common.

Pleural pain, especially with coughing, is common because the abscess is often subpleural.

Weight loss, anemia, and pulmonary osteoarthropathy appear when the abscess becomes

chronic (8-12 weeks after onset)

Physical findings may be minimal. Consolidation due to pneumonitis surrounding the abscess is the most frequent finding. It is most often elicited over the upper lateral chest wall (axillary areas). Rupture into the pleural space produces signs of fluid.

**B Laboratory Findings** Sputum is foul-smelling and dirty gray or brown in anaerobic ("putrid") infections, greenish or yellowish with a "musty" but not offensive odor in pyogenic ("nonputrid") infections. Smear and cultures for tubercle bacilli are required especially in lesions of the upper lobe and in chronic abscess.

Routine and anaerobic sputum cultures are of aid in selection of appropriate antibiotic therapy. Blood cultures may reveal septic embolization as a source of lung abscess.

**C X-ray Findings** A dense shadow is the initial finding. A central radiolucency, often with a visible fluid level, appears as surrounding densities subside. Tomograms (section films) may be necessary to demonstrate cavitation.

Chest films may also reveal associated primary lesions (e.g., bronchogenic carcinoma, pulmonary infarction), allow accurate assessment of response to therapy, provide anatomic localization where surgery is contemplated, and give information on pleural complications.

**D Instrumental Examination** Bronchoscopy should be performed routinely, since up to 10% of lung abscesses are secondary to bronchogenic carcinoma.

### Treatment.

*Postural drainage and bronchoscopy are important to promote drainage of secretions.*

**A Acute Abscess** Intensive antibacterial therapy is necessary to prevent destruction of lung tissue. If the patient improves, long-term treatment (1-2 months) is necessary to assure a cure. If the patient fails to respond, surgery is indicated without delay.

**B. Chronic Abscess** Although some patients with chronic lung abscess can be cured with antibacterial agents, antibiotic therapy is most often employed as a means of reducing infection in preparation for surgery.

### Complications.

Rupture of pus into the pleural space (empyema) causes severe symptoms: increase in fever, marked pleural pain and sweating; the patient becomes "toxic" in appearance. In

chronic abscess severe and even fatal hemorrhage may occur. Metastatic brain abscess is a well recognized complication. Bronchiectasis may occur as a sequel to lung abscess even when the abscess itself is cured. Amyloidosis may occur if suppuration has continued for a long time.

### Prognosis

The prognosis is excellent in acute abscess with prompt and intensive antibiotic therapy. The incidence of chronic abscess is consequently low. In chronic cases surgery is curative.

**Brock R C** Lung Abscess. *Thomson* 1952  
**Fifer W R** & others. Primary lung abscess. Analysis of therapy and results in 55 cases. *Arch Int Med* 107:668-80, 1961.

## BRONCHOGENIC CARCINOMA

### Essentials of Diagnosis

- Insidious onset with cough, localized wheeze or hemoptysis, often asymptomatic.
- May present as an unresolved pneumonia or pleurisy with bloody effusion or as a pulmonary nodule seen on x-ray.
- Metastases to other organs may produce initial symptoms.
- Cytologic and bronchoscopic studies may confirm findings. Thoracotomy early if diagnosis is in doubt.

Differentiate from pulmonary tuberculosis, tuberculous bronchial stenosis or a primary infection or abscess which does not respond to antibiotics. Discrete nodules may require thoracotomy for diagnosis and differentiation from a granuloma or other solitary lesion.

### General Considerations

Cancer arising in the mucous membranes of the bronchial tree is the most common intra-thoracic malignancy. It occurs predominantly in men (81%) and may appear at any age, but most cases occur in the cancer age group (over 40).

The importance of genetic and environmental factors in the etiology of bronchogenic carcinoma is not known. However, the disease is rare in nonsmokers. The major bronchi are the site of origin of about 75% of the lesions. Local invasion of ribs, mediastinal structures and nerve plexuses and distant metastases to the liver, adrenals, kidneys and brain are common.

### Clinical Findings

**A Symptoms and Signs.** Persistent non-productive cough, hemoptysis and localized persistent wheeze are the major symptoms produced by bronchial irritation, erosion and partial obstruction (although there may be no symptoms). These are often attributed to cigarette cough or chronic bronchitis.

Pulmonary infections (pneumonitis, lung abscess) occurring distal to a bronchial obstruction frequently dominate the clinical picture and mask an underlying neoplasm. Any atypical pulmonary infection (persisting, recurring or responding incompletely to therapy) should suggest carcinoma.

Metastases frequently give rise to the first symptoms, e.g., bone or chest pain in osseous or pleural involvement, neurologic symptoms due to brain involvement. (No craniotomy without a chest film.)

In general, pulmonary signs result from the sequelae of bronchial obstruction: pleural involvement and mediastinal invasion. When a solitary small lesion does not produce significant bronchial obstruction or pleural involvement, there are no findings. If the lesion is large enough, there may be physical (and x-ray) signs of partial or complete bronchial obstruction with associated atelectasis and infection.

Clubbing of the fingers, nonpitting edema of the extremities and periosteal overgrowth (seen by x-ray) may appear rapidly with a localized carcinoma and regress spectacularly following surgical removal.

Local spread is characterized by pleural fluid (bloody effusion is commonly present), signs of mediastinal invasion (pericardial effusion, hoarseness and brassy cough, stridor, dysphagia) and signs of extension to neck structures. Bronchogenic carcinomas in the upper part of the lung may produce Pancoast's syndrome (ipsilateral Horner's syndrome and shoulder-arm pain).

Particular attention must be paid to involvement of supraclavicular nodes and the development of liver nodules, both common sites of metastases. Careful neurologic examination must be performed for evidence of brain metastases.

**B Laboratory Findings.** (The definitive stage of diagnosis.)

1. Sputum cytology. In the hands of an expert cytologist, a positive diagnosis of bronchogenic carcinoma can be made in 50 to 60% of cases on the basis of sputum cytology. Several specimens should be studied.

2. Bronchoscopy. Visualization and biopsy of the tumor is possible in 75% of cases; diagnosis is extended to over 80% with cytologic studies of bronchial washings.



3. Biopsy of the supraclavicular fat pad may reveal lymph nodes containing metastatic carcinoma.

4. Exploratory thoracotomy may be the only way to establish the nature of a mass when other studies are negative. The risk is small in the hands of an experienced thoracic surgeon.

**C. X-ray Findings:** The chest film offers the greatest possibility of early diagnosis and cure. Solitary nodules which do not cause symptoms or signs can be detected only by this method. Thirty to 60% of these "coin" lesions have proved to be carcinomas at thoracotomy.

The follow-up investigation of a pulmonary infection should include search for evidence of delayed or incomplete resolution, associated masses, and hilar lymph node enlargement. Chest films at weekly intervals are mandatory for infections not responding satisfactorily to therapy.

#### Treatment.

Early detection and surgical removal offer the only hope of cure. For this reason, a routine chest x-ray once a year for all men over 40 is strongly recommended. Symptoms due to inoperable lesions may be temporarily controlled by nonoperative means.

#### Prognosis.

Early diagnosis is important if the lesion is to be found in an operable stage. At present only about 10% of patients are alive 5 years after diagnosis.

Mayer, E., & H.C. Maier: *Pulmonary Carcinoma: Pathogenesis, Diagnosis and Treatment*. Lippincott, 1956

Shaw, R.R., & D.L. Paulson: *Treatment of Pulmonary Neoplasms*. Thomas, 1959.

Umlker, W.O.: *Diagnosis of bronchogenic carcinoma. An evaluation of pulmonary cytology, bronchoscopy, and scalene node biopsy*. *Dis. Chest* 37:82-90, 1960.

### BRONCHIAL ADENOMA

Bronchial adenoma (neoplasm arising in the glandular structures of the bronchial mucous membranes) is the most common (80%) "benign" bronchopulmonary neoplasm, and constitutes 5-10% of solitary pulmonary nodules. Sex distribution is equal, age incidence is somewhat lower than that of bronchogenic carcinoma. It is locally invasive.

The great majority of bronchial adenomas arise in the proximal bronchi. The onset is insidious. Cough and localized wheeze are similar to those of bronchogenic carcinoma. These tumors are quite vascular, hemoptysis is probably the most common complaint.

Since bronchial adenoma does not tend to exfoliate, sputum examination is not helpful. Differentiation from bronchogenic carcinoma thus depends upon bronchoscopic biopsy or exploratory thoracotomy.

In many cases bronchial adenoma can be distinguished from bronchogenic carcinoma only by histologic and cytologic study. Distinguishing also from other benign obstructions, e.g., foreign body, tuberculous bronchial stenosis.

#### Treatment.

Pedunculated and locally noninvasive adenomas may sometimes be removed by bronchoscopy. It is usually necessary to perform an exploratory thoracotomy and remove the neoplasm surgically.

The prognosis is good. The tumor tends to be locally invasive, but 5-10% metastasize slowly. Fatalities are not usually due to metastases but are associated with bronchiectasis, pneumonitis, hemorrhages, the complications of surgery, or asphyxiation secondary to obstruction by the tumor.

Overholt, R.H., Bougas, J.A., & D.P. Morse: *Bronchial adenoma: a study of 60 patients with resection*. *Am. Rev. Tuberc.* 75:865-84, 1957

### BRONCHIOLAR CARCINOMA (Alveolar Cell Carcinoma, Pulmonary Adenomatosis)

Bronchiolar carcinoma is a relatively uncommon pulmonary malignancy (1-5% of lung cancers) which grows slowly and metastasizes late. In contrast to bronchogenic carcinoma, it is often bilateral. Pulmonary architecture is not altered. The neoplastic cells line the alveoli and bronchioles. Sex distribution is equal. Most cases occur in the age group from 50-60.

Since this neoplasm originates in the bronchiolar or alveolar lining, the major bronchi are not involved and symptoms develop late. Copious watery or mucoid sputum is the major sign. With widespread lung involvement, dyspnea, cyanosis, dullness to percussion, clubbing, and cor pulmonale develop.

Cytologic examination of sputum is valuable since this tumor commonly exfoliates.

The usual x-ray picture is of bilateral multiple lung nodules or areas of consolidation (or both), but solitary nodules may be present and calcification may occur.

The bilateral occurrence, long survival, and relative absence of symptoms help distinguish bronchiolar carcinoma from bronchogenic carcinoma and bronchial adenoma; however bronchiolar carcinoma may present as a single nodule and with calcification, thus requiring differentiation also from tuberculomas, metastatic lesions, and mycotic infections (granulomas).

#### Treatment.

If involvement is unilateral and there is no evidence of extrapulmonary extension, surgical excision may be warranted.

#### Prognosis.

With treatment survival may be up to 6 or 7 years. Widespread pulmonary involvement is the usual cause of death. Metastases occur in 50% of cases.

Sochocky, S. Alveolar cell carcinoma. A review with a report of four cases. *Am Rev Tuberc.* 79:502-11, 1959

## SILICOSIS

#### Essentials of Diagnosis

- History of exposure to dust containing silicon dioxide (e.g., hard-rock mining, sandblasting)
- Characteristic x-ray changes. Bilateral nodules, fibrosis, hilar lymphadenopathy
- Recurrent respiratory infections
- Note: Tuberculosis is a common complication

Differentiate from other pneumoconioses (history of specific exposure), mycotic infections, neoplasms, and sarcoidosis.

#### General Considerations.

The pneumoconioses are chronic fibrotic pulmonary diseases caused by inhalation of inorganic occupational dusts. Free silica (silicon dioxide) is by far the most common offender.

#### Clinical Findings

A. Symptoms and Signs. Symptoms may be absent or may consist only of unusual suscep-

tibility to upper respiratory tract infections, "bronchitis," and pneumonia. Dyspnea on exertion is the commonest presenting complaint. It may progress slowly for years. Cough usually develops and is dry initially but later becomes productive, frequently with blood-streaked sputum. Severe hemoptysis may occur.

Physical findings may be absent in patients with advanced silicosis, who may be afebrile and well-nourished.

B. Laboratory Findings. Sputum studies for acid-fast bacilli are indicated to rule out silicotuberculosis.

C. X-ray Findings. Chest x-rays are not diagnostic but often strongly suggest the diagnosis. Abnormalities are usually bilateral, symmetric, and predominant in the inner mid-lung fields. Small nodules tend to be of uniform size and density. Enlargement of hilar nodes is a relatively early finding. Fibrosis is manifested by fine linear markings and reticulation. Coalescence of nodules produces larger densities. Associated emphysema gives an x-ray picture of increased radiolucency, often quite striking at the lung bases.

#### Treatment.

No specific treatment is available. Symptomatic treatment is indicated for chronic cough and wheezing. When tuberculosis occurs antituberculous drugs must be continued for life.

#### Prognosis

Gradually progressive dyspnea may be present for years. The development of complications especially tuberculosis markedly worsens the prognosis.

Morrow, C. S., & A. C. Cohen. The pneumoconioses. *M Clin North America* 43:171-89, 1959

## OTHER PNEUMOCONIOSES

The following substances, when inhaled, cause varying degrees of pulmonary inflammation, fibrosis, emphysema, and disability, usually to a lesser degree than silicon dioxide, coal dust, bauxite (aluminum and silicon), asbestos (dehydrated calcium-magnesium silicate), mica dust (aluminum silicates), talc (hydrous magnesium silicate), graphite (crystallized carbon plus silicon dioxide), beryllium and diatomaceous earth. The latter is almost

## Pneumoconioses\*

Disease and Occupation	Causative Particle and Pathology	Clinical Features	X-ray Findings
Silicosis (mining, drilling, blasting, grinding, abrasive manufacture)	Free silica ( $\text{SiO}_2$ , particle size about $3\ \mu$ ), causing lymphatic blockage, nodules, emphysema, infection, fibrosis.	Required exposure is 2-20 years. Dyspnea on exertion, dry cough. Frequent infections, especially tuberculosis. Pulmonary insufficiency, chronic cor pulmonale.	Hilar adenopathy, nodules (inner, mid lung fields), over-all increased radiolucency, fibrosis. Signs of associated tuberculosis.
Asbestosis (asbestos mining and processing)	Magnesium silicate (particle size 10-200 $\mu$ ), rod-shaped bodies visible in tissue sections and sputum, causing obstruction of bronchioles, distal atelectasis, fibrosis (little nodulation).	Required exposure 2-8 years. Dyspnea early. Productive cough. Pulmonary insufficiency. Corns on skin of extremities (imbedded particles). Possible increased incidence of bronchogenic carcinoma.	Fine reticular markings in lower lung fields. Thickening of pleura ("ground glass" appearance), obliteration of costophrenic angles.
Berylliosis (beryllium production, manufacture of fluorescent powders)	Beryllium particles. Acute Patchy infiltrations, resembling bronchial pneumonia. Chronic Fine nodules, "lace-work" fibrosis, slight hilar adenopathy.	Acute After a few weeks of exposure, upper respiratory symptoms, "bronchitis," "pneumonia" later. Chronic Required exposure 6-18 months. Dyspnea, cough, weight loss, cyanosis. Various skin lesions, pulmonary insufficiency, cor pulmonale.	Acute Clear at first, then patchy infiltrations. Chronic Scattered minute ("sandpaper") nodules. Later, larger nodules, diffuse reticular markings. Slight hilar adenopathy.
Bauxite pneumoconiosis (Shaver's disease) (production of fused aluminum)	Aluminum (particle size 0.02-0.5 $\mu$ ), causing hilar adenopathy, fibrosis, atelectasis, emphysema.	Required exposure is several months to 2 years. Dyspnea (marked pulmonary insufficiency). Attacks of spontaneous pneumothorax.	Hilar and mediastinal adenopathy, irregularity of diaphragms, fibrosis, emphysema.
Anthraxosis (rarely dissociated from silicosis) (mining, city dwellers)	Coal dust, causing black discoloration of lungs, nodes, distant organs (nodules rare).	Progressive disease (fibrosis, emphysema) reported in Welsh soft-coal workers. Small quantities of silica may be an important factor.	"Reticulation," fine nodules. Coal dust per se probably does not produce the large densities seen in silicosis.
Siderosis (iron ore processing, metal drilling, electric arc welding)	Iron oxides, metallic iron, causing "red" (oxides) and "black" (metallic) discoloration of lung. "Red" type leads to fibrosis. "Black" type associated with silicosis.	Symptoms are those of associated silicosis.	Dependent mainly on associated silicosis.

\*Actual exposure is rarely to one dust alone.

pure silicon dioxide and produces effects essentially like those of silicosis.

Identification of these pulmonary dust diseases depends upon a careful inquiry into possible occupational or casual exposure.

Treatment is symptomatic.

See references under Silicosis

## PULMONARY ATELECTASIS

### Essentials of Diagnosis

- Acute sudden marked symptoms of dyspnea cyanosis, fever even if area is small
- Chronic almost no symptoms even if area is large
- Mediastinal shift toward involved side diaphragm up, narrowing of intercostal spaces
- Homogeneous density on x-ray

Distinguish from lobar pneumonia  
pulmonary infarction pneumothorax  
and other pulmonary infections

### General Considerations

Pulmonary atelectasis is a collapse and nonaeration of lung segments distal to a complete bronchial obstruction produced by a wide variety of diseases. A clinical history consistent with retention of secretions, aspiration of a foreign body, or bronchial infection can usually be obtained.

Postoperative atelectasis is the most common variety (occurs in 2-5% of patients after major surgery). The onset is usually 24-72 hours after operation.

Bronchial obstruction prevents entry of air into the distal segment lobe or even the entire lung ("massive atelectasis").

Compensatory changes occur to "fill in the space" previously occupied by the collapsed lung: (1) shift of the mediastinum toward the side of collapse, (2) upward displacement of the diaphragm on the involved side, and (3) overexpansion of remaining lung tissue on both sides ("compensatory emphysema").

Compression of the lung from without (e.g., pleural effusion) is of far less physiologic significance than atelectasis due to obstruction.

### Clinical Findings.

**A. Symptoms and Signs.** The severity of symptoms depends upon the site of obstruction and the rate at which it develops, and the pres-

ence or absence of infection in atelectatic area. The more acute the onset (e.g., postoperative atelectasis), the more marked the symptoms. Massive collapse in acute atelectasis causes marked dyspnea, cyanosis, tachycardia, chest pain, and fever. Lesser degrees of collapse produce variable symptoms, but even a small acute atelectasis may produce symptoms.

Symptoms, e.g., wheezing and cough are often due to the obstruction itself or to infection distal to the block.

The physical findings in acute atelectasis include marked decrease of chest motion on the affected side, with narrowing of intercostal spaces, displacement of the mediastinum to the involved side, as shown by the shift of the trachea, cardiac apex, and dullness, percussion dullness, and decreased to absent vocal fremitus. Breath sounds, and voice sounds, bronchial breath sounds are occasionally present over the atelectatic area and may alternate with diminished breath sounds.

In chronic atelectasis, displacement of the mediastinum is modified by the alowness of compensatory changes, rigidity of the mediastinum due to the underlying disease, and changes of the elasticity of the surrounding diseased lung.

**B. X-ray Findings.** The collapsed segment is visible as a homogeneous "ground glass" density. The atelectatic portion of lung is denser than a comparable area of consolidation because no air is present with the fluid. The volume of the collapsed lobe diminishes markedly. The diaphragm is displaced upward on the side of the collapse. Mediastinal shift to the involved side is a major diagnostic feature. Pleural fluid is not infrequently noted on the affected side, but it fails to displace the mediastinum back to the midline and the fluid line is seen to run downward and laterally from the midline instead of upward and laterally (as in fluid without atelectasis).

**C. Instrumental Examination.** Bronchoscopy is very helpful in diagnosis and treatment.

### Complications.

The sequelae of unrelieved obstruction with atelectasis are infection, destruction of lung tissue with fibrosis, and bronchiectasis.

### Treatment.

**A. Postoperative Atelectasis.** Force the patient to cough and to hyperventilate, either voluntarily or by use of a mixture of 95% oxygen and 5% CO<sub>2</sub> administered by mask for several minutes every 1-3 hours. (This is also a good preventive measure.)

Bronchodilatation by aerosol with intermittent positive pressure (e.g., Bennett valve) has been demonstrated to resolve many cases of postoperative atelectasis. The apparatus should be used for 30 minutes every 2-3 hours for 24 hours before deciding that other measures are necessary.

Aspiration of the tracheobronchial tree with a soft rubber catheter passed blindly through the nasopharynx or with the aid of a laryngoscope is often effective.

If the above fail or atelectasis is massive, aspiration of mucus by bronchoscopy is indicated.

Give procaine penicillin G, 300,000 units I.M., twice daily.

**B. Spontaneous Atelectasis** Bronchoscopy is indicated to determine the nature of the obstruction and to institute appropriate treatment.

### Prognosis.

Although the outlook is usually good, unrelieved collapse may result in death (when massive) or in prolonged morbidity (when lobar or segmental).

Langston, H.T., Pantone, A.M., & M. Melamed: *The Postoperative Chest*. Thomas, 1958.

## CHRONIC PULMONARY EMPHYSEMA

### Essentials of Diagnosis

- Insidious onset of exertional dyspnea, no dyspnea at rest or orthopnea.
- Wheezing is common.
- Productive cough, often ineffective in clearing the bronchi.
- Barrel chest, use of accessory muscles of respiration.
- Over-aerated lung fields and flattened diaphragm on chest x-ray.

Dyspnea must be differentiated from that due to congestive heart failure.

### General Considerations.

Emphysema is characterized by diffuse distention and over-aeration of the alveoli, disruption of intra-alveolar septa, loss of pulmonary elasticity, increased lung volume, and associated impairment of pulmonary function due to disturbed ventilation and altered gas and blood flow.

Emphysema may occur (1) in the absence of a history of preceding chronic lung disease

(etiology is unknown, although an inherent defect in pulmonary elastic tissue has been suggested), (2) secondary to chronic diffuse bronchial obstruction (e.g., asthma, bronchitis) or (3) in association with fibrotic pulmonary disease (e.g., silicosis, fibrosis). There is no justification for the view that glass-blowing, wind-instrument playing, and similar occupations cause emphysema. Many investigators feel that cigarette smoking is a major cause.

Emphysema is the most common cause of chronic pulmonary insufficiency and chronic cor pulmonale. It is predominantly a disease of middle-aged men.

Localized and microscopic areas of emphysema occur in many pulmonary diseases. The entity considered here refers to a diffuse process in which emphysematous changes are the predominant pathologic feature.

### Clinical Findings.

**A. Symptoms and Signs** The diagnosis of physiologically significant emphysema depends upon a history of exertional dyspnea and chronic productive cough (the most frequent presenting symptoms). Onset is usually insidious. Dyspnea at rest and orthopnea are unusual even with advanced emphysema (except with superimposed acute bronchial disease). Productive cough is common. Cough is frequently aggravated by intercurrent respiratory infections. Bouts of wheezing are not unusual. Minor respiratory infections which would be of no consequence to patients with normal lungs can produce fatal or near-fatal disturbances of respiratory function in the patient with emphysema.

Weakness, lethargy, anorexia, and weight loss are due to hypoxia, the increased muscular activity required for breathing, and respiratory acidosis.

The chest is maintained in a fixed inspiratory position ("barrel-shaped") with increased anteroposterior diameter. The neck appears shortened. Accessory muscles of respiration (sternomastoids, pectorals, scaleni) are employed along with overuse of abdominal and upper intercostal muscles. Palpation confirms decreased costal motion, with a tendency of the entire thorax to move vertically as a unit. Diffuse hyperresonance, especially at the bases, masks the normal cardiac and hepatic dullness. Descent of diaphragms is decreased to absent. Breath sounds are diminished, with a prolonged and high-pitched expiratory phase. Scattered musical wheezes and rhonchi are frequently present.

The liver is depressed by the flattened diaphragm and may be palpable 2-3 cm. below the costal margin. The lips and nail beds are

**cyanotic** The face is frequently ruddy to ruddy-cyanotic reflecting anoxia and compensatory polycythemia. Clubbing of the fingers and toes is occasionally encountered along with other manifestations of pulmonary osteoarthropathy.

Peripheral edema and venous distention occur if right heart failure (cor pulmonale) is present.

**B X ray Findings** Hyperinflation of lung fields is most marked at the bases and behind the sternum. The anteroposterior chest diameter is increased. Low flat diaphragms move poorly on fluoroscopy. Bullae may appear as annular transparencies occasionally of immense size.

Bronchograms may reveal a loss of the normal delicate "tree-in-full bloom" pattern of the terminal bronchioles.

**C Laboratory Findings** Vital capacity may be normal in emphysema even though extensive disease is present. Increased residual air volume is the most characteristic abnormality, but its determination is not a clinical procedure. A reduction in the timed vital capacity is a simple and direct measure of air trapping.

RBC and packed cell volume may be increased (polycythemia) but marked polycythemia is not a frequent finding in emphysema.

### Complications

Recurrent acute suppurative infections of the bronchioles are manifested by increase in dyspnea, cyanosis, fever, and the production of purulent sputum. Such infections are a grave matter in patients with poor pulmonary function.

Indiscriminate prolonged administration of oxygen to patients in respiratory acidosis may remove the last remaining stimulus to respiration, i.e., hypoxia, resulting in hypoventilation, increasing acidosis, and coma.

Spontaneous pneumothorax may result from rupture of an emphysematous bleb into the pleural space.

Congestive right heart failure may result from chronic emphysema, worsening the prognosis.

### Treatment

**A Specific Measures** Since many patients have an associated chronic bronchitis with some elements of spasm, therapy is generally similar to that outlined for chronic bronchitis or chronic bronchial asthma.

1. Bronchodilators to relieve bronchial spasm.

2. Eradicate any infection - Give specific antibiotics (or tetracycline if bacterial sensitivity cannot be determined). Prolonged therapy may be necessary.

3. If the above measures fail to relieve bronchial spasm, corticosteroids may give dramatic relief. They should be used in minimum dosage with careful attention to the dangers and precautions outlined in Chapter 17.

### B General Measures

1. **Oxygen Inhalation** is often necessary but must be used cautiously and the patient observed frequently to prevent hypoventilation and coma due to  $\text{CO}_2$  retention. Oxygen can be given safely by the intermittent positive pressure method since this also produces adequate ventilation and removes  $\text{CO}_2$ . Where marked hypoventilation is already present, an automatic cycling device or manual cycling of the apparatus is necessary.

Tracheostomy should be used early in critical patients to improve ventilation and permit removal of secretions.

2. **Maintain optimal mechanical efficiency of the diaphragm.** Exercises to strengthen the abdominal muscles and permit more complete exhalation should be encouraged. Overdistention of lungs can often be temporarily relieved by the following maneuver. The patient places the palms of both hands under the anterior ribs and pushes inward and upward during the end of expiration. This is repeated 10-15 times 2-3 times daily. Patients often state that their dyspnea is relieved for hours in this way.

### Prognosis

The prognosis for morbidity and mortality depends upon the extent of pulmonary insufficiency, which is best judged by the patient's tolerance for exercise and by pulmonary function studies.

Barach A L, & H A Bickerman (editors)  
**Pulmonary Emphysema** Williams & Wilkins 1956

Loenhardt, K O. Resuscitation of the moribund asthmatic and emphysematous patient. *New England J Med* 264:785-90, 1961.

Richards, D W, Jr. Pulmonary emphysema: etiologic factors and clinical forms. *Ann Int Med* 53:1105-20, 1960.

## THE ALVEOLAR-CAPILLARY BLOCK SYNDROME

This clinical syndrome, due to impaired oxygen-diffusing capacity of the lungs, occurs

in a variety of diseases which involve the alveolar-capillary interface. Prominent among these are sarcoidosis, berylliosis, scleroderma, miliary tuberculosis, idiopathic fibrosis and granulomatosis, mitral stenosis, and asbestosis.

The principal clinical features are hyperventilation, tachypnea, dyspnea, cyanosis, and basal rales. Signs of bronchial obstruction (e.g., wheezing) are usually absent. Chest films almost always reveal striking and diffuse infiltration.

Precise definition is made by pulmonary function tests, which reveal the following:

(1) Anoxemia, (2) normal or decreased arterial CO<sub>2</sub> tension, (3) uniform reduction in lung volume with normal residual volume/total lung capacity ratio, (4) well-preserved maximal breathing capacity, and, especially, (5) decreased diffusing capacity.

Treatment is directed at the underlying cause of the impaired oxygen diffusion. If this is reversible, improvement can be anticipated. Miliary tuberculosis and some forms of pulmonary edema are reversible with appropriate treatment. Diffuse pulmonary sarcoidosis in its acute form and some types of nonspecific granuloma respond dramatically to corticosteroid drugs. When fibrosis is well established, improvement usually does not occur.

When oxygen is required it is best given by an intermittent positive pressure method

Boden, M. E., & R. A. Boden: The alveolar-capillary block syndrome. Editorial. *Am J. Med.* 24:493-6, 1958.

## PULMONARY EMBOLISM

### Essentials of Diagnosis

- Sudden onset of dyspnea, cough, and pleuritic pain.
- Hemoptysis, friction rub.
- X-ray density, transient right ventricular strain pattern on ECG.
- Often a history or findings of thrombophlebitis.

Differentiate from myocardial infarction. Pulmonary infiltrates do not occur in myocardial infarction, although the 2 conditions frequently coexist. Differentiate also from pneumonia and atelectasis, which have similar pulmonary infiltrates.

### General Considerations.

Most emboli arise from thromboses in the deep veins of the lower extremities. (Emboli of air, fat, and tumor cells are not discussed here.) This event is so common in the older, bedridden, or postoperative patient that any sudden appearance of pulmonary or cardiac symptoms and signs in such patients should at once suggest this diagnosis.

Important factors which predispose to the formation of deep vein thromboses (i.e., of pulmonary emboli) include age (people over 40 most frequently affected) confinement to bed, cardiovascular disease (especially congestive failure and myocardial infarction), obesity, postoperative state (especially extensive pelvic and abdominal surgery), postpartum state, and severe trauma.

Emboli arising from thrombi of the upper extremities and the right heart are uncommon. There is evidence that the consequences of pulmonary embolism are more severe in a lung which has been the site of previous congestion (e.g., congestive failure). The occurrence of embolization while straining at stool, rising from a chair, etc., suggests a "mechanical" factor in dislodging emboli from thrombi.

There is evidence that thrombi may arise in situ in cardiac disease with congestion of the lungs.

### Clinical Findings.

The clinical and laboratory manifestations of pulmonary embolism depend largely on the level at which the obstruction occurs, hence on the size of the embolus. In a terminal artery the findings may be minimal or absent, in a medium-sized artery, predominantly pulmonary symptoms and signs and x-ray densities; in a large artery, predominantly cardiac signs, distention of neck veins and liver, and ECG changes, progressing to shock, syncope, cyanosis, and sudden death. The latter symptoms and signs are those of the embolism *per se*, hemoptysis, pleuritic pain, and infiltrates on x-ray result from lung infarction, and appear 12-36 hours after embolism.

The source of a pulmonary embolus is frequently clinically "silent."

**A. Symptoms and Signs:** These are characteristically sudden and episodic, interspersed with "silent" intervals. Chest pain (present in 75% of cases) may be pleuritic or anginal (not dependent upon pre-existing coronary disease). Dyspnea (50% of cases) varies from mild wheezing to frank pulmonary edema.

Sudden dyspnea in the absence of obvious evidence of cardiac or pulmonary disease is a characteristic of pulmonary embolism. Cough occurs in about 30% of cases, hemoptysis in about 25%. Syncope is a much more frequent symptom in pulmonary embolism than in acute myocardial infarction.

Temperature commonly (70%) rises sharply at the onset of symptoms; this may be the sole manifestation of pulmonary embolism. Shaking chills are rare.

Cardiac signs include tachycardia (50%) prominent pulsations in the second and third left intercostal spaces (rare), accentuation of the second pulmonary sound, loud systolic murmur, protodiastolic gallop, vascular collapse (shock), and cyanosis.

Pulmonary signs which may be transient include rales, signs of consolidation, pleural friction rub, and (occasionally) signs of pleural fluid.

**B Laboratory Findings.** Moderate leukocytosis occurs in 70% of cases, hyperbilirubinemia in 50%. The sedimentation rate is elevated.

**C X-ray Findings.** Abnormalities usually result from pulmonary infarction; they may not appear for several days. Clouding at the base of the lung, obscuring the costophrenic angle, may be an early sign. A wedge-shaped density with the base against a pleural surface is the classical infarct shadow but oval, round, or irregular densities are more frequently encountered. Pleural effusions, usually small, are frequent.

**D ECG Findings.** These are often transient, evolve rapidly in at least 10-20% of cases, and would probably be encountered oftener if more frequent tracings were obtained. Standard leads show a deep S in lead I, prominent Q with inverted T in lead III, tall P in lead II (occasionally), and right axis deviation. Precordial leads show inverted T waves in  $V_1$ , transient incomplete right bundle branch block, prominent R waves over the right precordium, and displacement of the transitional zone to the left (clockwise rotation).

#### Treatment

Whenever a patient has a pulmonary embolism, suspect venous thrombosis and institute immediate therapy.

##### A Emergency Measures

1 Give oxygen in high concentration (preferably 100%) by mask to overcome anoxia. This also helps prevent cardiorespiratory failure.

2 Combat pulmonary arteriolar spasm with papaverine hydrochloride 30-60 mg ( $\frac{1}{2}$ -1 gr) and atropine sulfate 0.6-1 mg ( $\frac{1}{100}$ - $\frac{1}{60}$  gr) I.V. slowly, and repeat every 3-4 hours.

3 For severe pain, give meperidine hydrochloride (Demerol<sup>®</sup>) 50-100 mg subcut. I.V. or morphine sulfate 8-15 mg ( $\frac{1}{8}$ - $\frac{1}{4}$  gr) subcut. or I.V. These agents should be avoided in the presence of shock.

4 Treat shock, if present, with vasopressor drugs such as levarterenol bitartrate (Levophed<sup>®</sup>) 4 mg/L or metaraminol bitartrate (Aramine<sup>®</sup>) 15-100 mg in 500 ml 5% dextrose solution I.V. Adjust the rate of infusion to maintain the systolic pressure at about 90 mm Hg.

5 Anticoagulant therapy should be started to prevent additional thrombus formation.

**B Follow-up Treatment.** Observe carefully for secondary infection and institute antibiotic treatment promptly if signs occur. If pleural effusion occurs and embarrasses respiration, remove fluid by paracentesis.

#### Prognosis

Pulmonary embolism is a common cause of sudden death. The prognosis is grave when acute cor pulmonale or vascular collapse (shock) occurs. Recovery from small emboli is frequent. The mortality rate rises with each episode of embolism.

Gorham L.W. A study of pulmonary embolism. Parts I, II, and III. Arch Int Med 108:8-22, 1961.

## DISEASES OF THE PLEURA

### FIBRINOUS PLEURISY

Deposition of a fibrinous exudate on the pleural surface is the cardinal pathologic feature of fibrinous pleurisy. This is usually secondary to a pulmonary disease, pneumonia, pulmonary infarction, and neoplasm are the most frequent causes. Fibrinous pleurisy may precede the development of pleural effusion.

Chest pain is typically pleuritic, i.e., it is greatest during inspiration. Pain is minimal or absent when the breath is held or when the ribs are splinted. Referred pain may occur from the diaphragmatic pleura to the shoulder and neck (central diaphragm) or upper abdomen (peripheral diaphragm).



Pleural friction rub ("to-and-fro," "squeaky-leather" or "grating" sounds) with respirations is pathognomonic. It may occur without pleuritic pain and vice versa. Splinting of the involved chest is characteristic, with decreased motion and shallow, "grunting" respirations. The patient lies on the painful side. Other findings reflect the underlying pulmonary disease.

Treatment is aimed at the underlying disease. The treatment of the pleurisy consists only of relieving pain. Analgesics and ethyl chloride spray may be used as necessary. Strapping the chest with adhesive tape may give relief by restricting movement. Procaine intercostal block may be used in more severe cases.

Fibrinous pleurisy clears promptly with the resolution of the primary process. Pleural scars may remain and create minor diagnostic difficulties on future chest x-rays.

## PLEURAL EFFUSION

### Essentials of Diagnosis

- Dyspnea if effusion is large, may be asymptomatic.
- Decreased breath sounds, flatness to percussion, egophony.
- The underlying cardiac or pulmonary disease may be the major source of symptoms and signs.
- X-ray evidence of pleural fluid.

Every effort should be directed toward the diagnosis of the primary disease, e.g., neoplasm, cardiac failure, tuberculosis, pneumonia. "Idiopathic" pleural effusion often proves to be of tuberculous origin.

### General Considerations.

Any fluid collection (transudate or exudate) in the pleural space constitutes a pleural effusion. Because there is considerable variation in the type of effusion produced by a given disease, diagnostic rules such as, "tuberculous effusions are never bloody," are of statistical significance but are not binding upon the diagnostic evaluation of individual cases.

Numerous disease processes of inflammatory, circulatory, and neoplastic origin can cause pleural effusion.

### Clinical Findings.

A. Symptoms and Signs. There may be no symptoms. Chest or shoulder pain may be

present at onset, especially when fibrinous pleurisy precedes the effusion. Dyspnea may be mild or, with large or rapidly forming effusions, prominent. Cardiac dyspnea may be associated with effusion. Fever, sweats, cough, and expectoration may occur, depending upon the underlying cause.

Physical findings include decreased motion of the chest and decreased to absent vocal fremitus on the side of the fluid, flat percussion note and decreased to absent breath sounds over the fluid, and egophony ("e"-to-"a" sound) at the upper level of the fluid. With large effusions the mediastinum shifts away from the fluid (as shown by displacement of the trachea and the cardiac apex) although underlying atelectasis may result in a shift toward the fluid. Signs resembling those of consolidation (dullness, bronchial breath sounds, bronchophony) are occasionally elicited over the fluid, presumably as a result of compression of the underlying lung by large, rapidly forming effusions.

B X-ray Findings. 300 ml. or more must be present before fluid can be demonstrated by x-ray. Obliteration of the costophrenic angle is the earliest sign. Later, a homogeneous triangular density with a concave medial border extends upward to the axilla, other borders are formed by the lateral chest wall and the diaphragm. The mediastinum shifts away from the fluid (displaced heart and tracheal air shadow). The mobility of the fluid shadow, which "pours" into dependent areas of pleural space when the patient is placed on the involved side, may aid in the demonstration of small effusions. An atypical distribution of fluid along the interlobar fissures or in loculated areas may be noted.

C Thoracentesis. This is the definitive diagnostic procedure. It demonstrates conclusively the presence of fluid, and provides samples for study of physical characteristics, protein content, cells, and infectious agents. Thoracentesis should be performed carefully to avoid introducing infection and puncturing the visceral pleura.

1. Removal of fluid for examination - Remove 50-500 ml. Use a two-way stopcock to avoid introduction of air. Care must be exercised to avoid contaminating the pleural space.

2. Pleural fluid examination - (Specimen must be fresh.) Take specific gravity to determine if the fluid is exudate or transudate. Smear and stain for the detection of organisms and nature of the cellular content. Collect a specimen with an anticoagulant for cell count. Culture on appropriate media and guin-

ea pig inoculation are indicated for all fluids from unexplained pleural effusions to demonstrate the presence of tubercle bacilli or fungi. Perform pathologic examination of a centrifuged button in suspected cases of malignancy.

**D Pleural Biopsy** This procedure has become very simple and valuable as a result of the development of better biopsy needles (e.g. Abrams needle) which permit thoracentesis and removal of one or more tissue specimens with the same needle. Pleural biopsy is indicated whenever the diagnosis is in doubt. If the tissue is not diagnostic, several more specimens should be taken.

#### Prevention of Post-pneumonic & Other Sterile Effusions

Preventive measures are directed at the primary disease. Begin or continue antibiotics as for treatment of pneumonia until the patient has been afebrile for 10-14 days or fluid is almost entirely resorbed.

#### Treatment

**A Post-pneumonic and Other Sterile Effusions** Remove readily obtainable fluid by multiple thoracentesis at daily intervals if necessary. Removal of more than 1000 ml at a time is not advisable. Reexamine pleural fluid to rule out empyema. If the pleurisy does not respond to treatment, bed rest is essential until the patient is afebrile.

**B Tuberculous Effusion** Uncomplicated primary effusion in a patient with a positive tuberculin skin test is treated essentially as minimal pulmonary tuberculosis. A course of isoniazid and aminosalicylic acid (PAS) or isoniazid and streptomycin is recommended. Bed rest is indicated as for minimal pulmonary tuberculosis. Removal of all readily available fluid by thoracentesis is advisable to minimize later thickened pleura. When high fever persists longer than 2 weeks, hematogenous dissemination should be suspected. Careful follow-up for 5 years is necessary because many patients with primary tuberculous effusions develop pulmonary tuberculosis later, usually within 5 years.

#### Prognosis

The prognosis is that of the underlying disease.

**Ungerleider J T** The diagnostic significance of pleural effusion. *Dis Chest* 32:83-92, 1957

### PLEURAL EMPYEMA (Nontuberculous)

Acute infection of the pleural space may result from (1) direct spread from adjacent bacterial pneumonia (especially pneumococci, streptococci and staphylococci), (2) rupture of lung abscess into the pleural space, (3) invasion from adjacent osteomyelitis (rib vertebral), (4) invasion from subphrenic infection or (5) traumatic penetration. The availability of early and specific therapy for these conditions has made empyema an uncommon disease.

The clinical findings are often obscured by the primary underlying disease. Pleural pain, fever and toxicity after clinical improvement of the primary disease in association with physical and x-ray signs of pleural fluid are characteristic. Thoracentesis reveals a frankly purulent exudate from which the etiologic organism may be cultured. Empyema-like lung abscess may become chronic with a prolonged course and little tendency to spontaneous resorption (especially in bronchiectasis and tuberculous).

The key to successful nonsurgical treatment of an acute empyema is early diagnosis. Any collection of fluid appearing in the course of a pulmonary inflammatory disease should be aspirated at once. If pus is present, a specimen should be obtained for culture. The fluid is then aspirated as completely as possible and irrigated with sterile physiologic saline solution until the irrigating solution returns clear. Aqueous penicillin (one million units) and streptomycin (0.5 Gm) in 10 ml of saline are left in the pleural space following the irrigation. Aspiration, irrigation and instillation of antibiotics are repeated daily until no further fluid can be obtained. When cultures of the pleural fluid are reported, the antibiotics may be adjusted accordingly. The same antibiotic is given parenterally or orally (or both) and should be continued for 10-14 days after the patient has become afebrile. (Caution: Prolonged use of streptomycin should be avoided because of the danger of eighth nerve damage.)

If the pus is initially too thick to be aspirated through a needle or if the patient's condition is worsening despite treatment, surgical drainage is indicated. Chronic empyema usually results from inadequately treated acute empyema or from a bronchopleural fistula. When the latter complication is present, surgical intervention may be required.

**Pecora D V** The surgical treatment of chronic pleural empyema. *J Thorac Surg* 36:92-101, 1958

## HYDROTHORAX

Hydrothorax (collection of serous fluid in a pleural space) is most often due to congestive cardiac failure. The findings are as in pleural effusion. Treatment is directed at the failure itself. When respiratory embarrassment occurs the fluid must be removed by thoracentesis.

The prognosis is that of the underlying disease.

## HEMOTHORAX

Hemothorax (pooling of blood in a pleural space) is most commonly due to trauma. The findings are as for pleural effusion. World War II experience has shown that aspiration and irrigation of the blood from the pleural cavity is the treatment of choice. Repeated aspirations are performed as necessary. If bleeding continues, thoracotomy is indicated. Great care must be taken during aspiration to avoid bacterial contamination of the pleural cavity. The proteolytic enzymes (see above) may be useful after bleeding has stopped. Surgical removal of residual blood clots may be necessary.

Fry, W., & others: The surgical treatment of spontaneous idiopathic hemopneumothorax. *Am. Rev. Tuberc.* 71:30-48, 1955

## SPONTANEOUS PNEUMOTHORAX

### Essentials of Diagnosis.

- Sudden onset of chest pain referred to the shoulder or arm on the involved side, associated dyspnea.
- Hyperresonance, decreased chest motion, decreased breath and voice sounds on involved side, mediastinal shift away from involved side
- Chest x-ray revealing retraction of the lung from the parietal pleura is diagnostic.

Spontaneous pneumothorax may be secondary to a diseased pleura (e.g., tuberculosis, neoplasm, abscess) or pulmonary disease (e.g., tuberculosis, bullous emphysema), but it is most com-

monly due to unexplained rupture of small blebs on the visceral lung surface. Chest pain must be differentiated from that of myocardial infarction (especially when there is shoulder-arm radiation), pulmonary embolism, and acute fibrinous pleurisy.

### General Considerations.

The cause of spontaneous pneumothorax is unknown in 80% of cases, but it may be secondary to pulmonary disease. The idiopathic form typically occurs in healthy young males with no demonstrable pulmonary disease other than the subpleural blebs usually found on thoracotomy or (rarely) autopsy.

Entry of air into the pleural space from a rent in the visceral pleura causes partial to complete collapse of the underlying lung. Collapse usually is self-limited by rapid sealing of the tear. Occasionally a "valve effect" occurs, with progressive entry of air on inspiration and failure of exit on expiration, and with increasing intrapleural pressure (tension pneumothorax). This has a profound effect on cardiorespiratory dynamics and may be fatal if not treated promptly.

Secondary pneumothorax may occur with involvement of the visceral pleural surface by disease (tuberculosis, neoplasm, abscess) or following rupture of a bulla which is part of a generalized emphysema.

The cause of bleb formation and the exact mechanism of rupture in idiopathic cases are not known.

Fifty per cent of cases occur in the age group from 20 to 24. 85% in men. Onset may occur during exercise or at complete rest.

### Clinical Findings.

**A. Symptoms and Signs.** Symptoms are occasionally minimal (vague chest discomfort, dry cough) or may even be overlooked. Characteristically, however, the onset is sudden, with chest pain referred to the shoulder and arm on the affected side. Pain is aggravated by physical activity and by breathing, producing dyspnea. Fever is usually not present. Shock and cyanosis occur in tension pneumothorax, where high intrapleural pressure interferes with venous return to the heart.

Physical findings consist of decreased chest motion and decreased to absent vocal fremitus and breath sounds on the affected side. (Breath sounds may be abnormally loud and harsh on the normal side.) The percussion note is hyperresonant over the involved side. With large pneumothorax, the mediastinum shifts away from the affected side and a metallic "close to" sound can be heard with the

stethoscope when one coin is tapped against another held to the affected side of the chest ("coin sign"). A "tapping sound" roughly synchronous with the heart beat is occasionally heard in left-sided pneumothorax.

**B X-ray Findings** Air in the pleural space with a visible border of retracted lung (difficult to see if the collapse is small) is best seen over the apex and in films taken in expiration. Retraction may be confined to one area of the lung (pleural adhesions in other areas). Contralateral shift of the mediastinum is demonstrated by displacement of the tracheal air shadow and cardiac apex. (Great amounts of air are present with tension pneumothorax.) Pleural fluid (bleeding from a ruptured area or torn adhesion) is occasionally visible but is seldom present in large quantity. Signs of an underlying pulmonary disease are seen on x-ray in fewer than 10% of cases.

#### Treatment.

**A. Emergency Measures for Tension Pneumothorax** Note This is a medical emergency. Insert a trocar or large bore, short-beveled needle into the anterior part of the affected chest (just into the pleural space to avoid trauma to the expanding lung). After tension has been relieved a simple one-way valve made from a rubber glove finger, slit at the end, can be tied to the hub of the trocar or needle. As soon as possible a rubber catheter should be introduced into the pleural space via a trocar and attached to a water trap with the end of the tubing under 1-2 cm of water. A suction pump (with a maximum vacuum of -30 cm of water) may be attached to the water trap.

If pain is severe give morphine sulfate, 8-15 mg. ( $\frac{1}{8}$ - $\frac{1}{4}$  gr.) I.V. or I.M. Treat shock if present (see p. 3).

Follow-up treatment is as for spontaneous pneumothorax.

**B Spontaneous Pneumothorax Without Increased Intrathoracic Pressure** Bed rest is essential until air has been largely resorbed. If tuberculosis is present, treat accordingly. Pleural pain should be treated with analgesics, strapping, or ethyl chloride spray (see p. 137). If there is no underlying pneumonitis and cough is annoying, codeine sulfate, 15-60 mg. ( $\frac{1}{4}$ -1 gr.) every 3-4 hours should be used. Aspirate air if dyspnea is present or if the pneumothorax space is large enough to aspirate safely. If air leakage continues, an intercostal catheter or an infusing needle (e.g., Clagett S needle) attached to a water trap and suction pump (see above) may be necessary. Administer oxygen if dyspnea is present. In some cases of spon-

taneous pneumothorax where the lung does not expand or if there are repeated episodes of collapse, exploratory thoracotomy may be necessary.

#### Prognosis.

The outlook is very good in "idiopathic" cases but is more serious in secondary cases because of the danger of infection of the pleural space. Recurrence occurs in 15-20%, usually on the same side. Hemothorax occurs in about 10% of cases. Empyema may occur where underlying disease, especially tuberculosis, is present. Failure of lung to re-expand, with fibrothorax, is rare in the idiopathic type.

Tension pneumothorax is a true emergency.

Briggs, J. N., Walters, R. N., & F. X. Bryan. Spontaneous pneumothorax. *Dis. Chest* 24: 564-70, 1953.

DuBose, H. M., Price, H. J., & P. H. Guilford. Spontaneous pneumothorax: medical and surgical management. *New England J. Med.* 248:752-6, 1953.

Rapport, R. L., Thurlow, A. A., & K. P. Glassen. Etiology and management of spontaneous pneumothorax. *Arch. Surg.* 67:266-75, 1953.

### TRAUMATIC PNEUMOTHORAX

**Note** This is an emergency. Open chest wounds (sucking wounds) must be made airtight by any available means (e.g., bandage, handkerchief, shirt, or other material) and closed surgically as soon as possible.

Traumatic pneumothorax due to lung puncture or laceration (fractured rib, bullet, etc.) is managed like spontaneous pneumothorax (above). Surgery is frequently required.

### DISEASES OF THE MEDIASTINUM

#### MEDIASTINAL MASS

Mediastinal masses are often clinically "silent" until they become large. They are frequently discovered on routine chest x-rays and fluoroscopy, where their position, density, and mobility are of aid in differential diagnosis. Biopsy is often the only way to make a differential diagnosis.

Because of their proximity to the heart, great vessels, esophagus, air passages, and surrounding nerves, even benign lesions are potentially serious.

The symptoms and signs are usually due to compression and distortion of surrounding structures. Pain is usually substernal. It originates in the afferent lower cervical and upper thoracic segments (may mimic "cardiac" pain), and occasionally radiates to the shoulder, neck, arms, or back. Cough suggests tracheal and bronchial involvement. Dyspnea is due to airway obstruction (which may lead to pulmonary infections). Respirations are stertorous, with suprasternal retraction on inspiration. Hoarseness is associated with compression paralysis of the thoracic portion of the left recurrent laryngeal nerve. Dysphagia is due to extrinsic compression of the esophagus with obstruction, it varies from mild to severe.

Compression of the heart or great vessels is an unusual cause of symptoms.

Tracheal shift is due to displacement by mass. Tracheal tug is associated with adjacent aortic aneurysms with transmitted pulsations.

The superior vena cava syndrome consists of dilated neck veins, fullness of the neck and face (collar of Stokes), and collateral veins on the thoracic wall. It is caused by compression of the superior vena cava.

Horner's syndrome (ipsilateral miosis, ptosis, and enophthalmos) is due to compression of sympathetic outflow pathways.

Chest x-ray and fluoroscopy may lead to the diagnosis. Lymph node biopsy of palpable (e.g., cervical, supraclavical) or nonpalpable (anterior scalent, paratracheal) nodes may be definitive. Exploratory thoracotomy is often necessary.

Treatment will depend upon the primary disease. The prognosis is variable, depending upon the cause and the histologic characteristics of the mass.

Lyons, H. A., Calvy, G. L., & B. P. Sammons.

The diagnosis and classification of mediastinal masses. 1. A study of 782 cases. *Ann Int. Med.* 51:897-932, 1959.

## PNEUMOMEDIASTINUM

### Essentials of Diagnosis.

- Sudden onset of severe retrosternal pain.
- Crepitus on palpation of neck and chest.
- Crunching sound simultaneous with heart beat.
- X-ray is diagnostic.

The pain may simulate that of myocardial infarction.

### General Considerations.

Free air in the mediastinum may be secondary to perforation of the intrathoracic esophagus or respiratory tract or may be caused by spontaneous rupture of an alveolus into the perivascular interstitial tissues of the lung. Air may also be sucked into the mediastinum through an open neck wound or from an area of emphysema in the neck resulting from a chest wound. Spontaneous pneumomediastinum is often associated with spontaneous pneumothorax, most often of the tension type.

### Clinical Findings

**A Symptoms and Signs** Symptoms are usually minimal. Typically, the air escapes into the subcutaneous tissues of the neck and then over the rest of the body and retroperitoneally. If pneumothorax (especially tension pneumothorax) is present also, there is usually a sudden onset of severe retrosternal pain radiating to the neck, shoulders, and anus (retroperitoneal diastension).

Dyspnea is not usually severe. Uncommonly high intramediastinal pressure results in compression of the heart and blood vessels with marked dyspnea, shock, and even death ("air block"). Hemodynamics are similar to those of pericardial tamponade.

Subcutaneous emphysema with crepitus on palpation of the skin of the neck or upper chest is common. Air may cause grotesque puffing of the neck and face.

"Crackling" or "crunching" sounds (Hamman's sign) in the substernal and precordial areas synchronous with the heart beat are characteristic, but are occasionally due to left-sided pneumothorax.

**B X-ray Findings** These are definitive, showing radiolucency surrounding the heart border and streaking of the upper mediastinum, and radiolucency of the retrosternal area on a lateral film taken at full expiration and in the subcutaneous tissue of the neck and shoulder areas.

### Treatment.

No treatment is usually required but a prompt search should be made for the underlying cause (e.g., pneumothorax, ruptured bronchus, perforated esophagus).

### Prognosis.

Spontaneous recovery is the rule. Unrelieved intramediastinal tension occasionally causes death.

### Differential Diagnosis of Mediastinal Masses

Metastases may occur in any portion of the mediastinum. Among infrequent mediastinal masses are thymus enlargement (superior), lipoma, pericardial cyst (anterior), meningocele and aneurysm of the descending aorta (posterior). Thymus enlargement is in the anterior superior mediastinum. It is physiologic in infants, usually malignant in adults. Benign enlargement is present in up to 15% of cases with myasthenia gravis.

Lesion	Density	Mobility (Fluoroscopy)	Clinical Features
Anterior Aneurysm ascending aorta	May show calcification	Vigorous expansile pulsation. Often dif- ficult to demonstrate	Pulsating mass may be palpable on the anterior chest wall. Ero- sion of vertebrae may produce back pain. Associated evidence of late syphilis is present.
Dermoid	Translucent upper area merging with denser underlying shadow. Presence of teeth or bone is pathognomonic. Tend to calcify.	May change in shape with respirations (fluid contents com- pressible)	Often clinically silent. Occa- sional rupture into bronchus with coughing up of hair and sebaceous material. May be associated with other congenital anomalies.
Substernal thyroid	Merges with soft tis- sues of neck. May have hazy calcification.	Moves with swallow- ing. Usually displaces trachea.	Upper portion is often palpable in the neck. Signs of thyro- toxicosis may be present.
Superior Broncho- genic cyst	May contain air over fluid (communication with bronchus)	May be seen to rise with swallowing.	May become infected, simulat- ing ordinary lung abscess.
Middle Lymphoma (Hodgkin's disease, lympho- sarcoma)	Dense, rounded masses. Usually bilateral.	May show transmitted pulsations when close to vessels. Relative- ly fixed.	Prominent systemic symptoms (e.g., Pel-Ebstein fever, cachexia, anemia, pruritus). Lymphadenopathy in palpable areas.
Posterior Neuro- fibroma	Close relationship to thoracic spine.	Fixed.	Often silent when discovered. Radicular pain may be promi- nent. Usually not associated with generalized neurofibroma- tosis (Von Recklinghausen). May produce compression of spinal cord.

Hamman L. Spontaneous mediastinal em-  
physema. Bull Johns Hopkins Hosp 64:1  
21, 1939.

### ACUTE MEDIASTITIS

Acute inflammation of the mediastinal space may be due to traumatic perforation of a thoracic viscus (e.g., during instrumentation or by lodged foreign bodies), spontaneous perforation of the esophagus (as in carcinoma) or

lymphatic and direct spread from an infection of the neck or head, e.g., retropharyngeal and cervical abscess.

Onset is usually within 24 hours after perforation. Findings include substernal and neck pain, progressive dysphagia, dyspnea, fever, chills, prostration and toxicity and signs of pneumomediastinum.

There may be no radiographic findings. Mediastinal widening is visible as a diffuse soft tissue density. Mediastinal mass (abscess) with or without a fluid level may be visible.

**Treatment.**

Treatment consists of large doses of penicillin and 1-2 Gm. of streptomycin daily. Surgical drainage in the cervical region is indicated when a collection of pus bulges in that area.

**Prognosis.**

Without treatment the mortality rate is high, with treatment, the prognosis is markedly improved.

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## OXYGEN THERAPY

Oxygen therapy consists of the administration of oxygen at concentrations greater than are found in the atmosphere. Increased concentrations are indicated only when hypoxia exists. The correction of hypoxia does not always require oxygen therapy, simple increase in tidal volume of air by mechanical assistance (see p 164) will remedy hypoxia caused primarily by hypoventilation. In fact, in some cases of hypoxia, oxygen therapy may be dangerous if not administered properly.

Oxygen therapy is always palliative. It is generally used to lide the patient over an emergency situation while the underlying cause is being corrected, correction may not always be possible. Whenever respiration ceases, resuscitation must be instituted.

**Dangers of Oxygen Therapy.**

The principal danger of oxygen therapy appears to be depression of respiration in severely hypoxic patients who have an elevation of  $\text{CO}_2$  tension or concentration in the blood. In these patients the respiratory center in the medulla has been "anesthetized" by the high  $\text{CO}_2$  tension. Respiration is under the control of the chemoreceptor centers, which are responsive to oxygen tension. When high concentrations of oxygen are given, the chemoreceptor centers are no longer stimulated and there is a resultant decrease in pulmonary ventilation, which may cause enough  $\text{CO}_2$  retention to produce narcosis, unconsciousness, and even death. This usually occurs within a few minutes after starting high concentrations of oxygen, but may occur up to 1-2 hours after instituting treatment. Therefore, no patient should be given oxygen unless he is under close observation during the first 30 minutes of oxy-

gen administration. Any patient with suspected elevation of  $\text{CO}_2$  tension should have a nurse in constant attendance, and some method of mechanical resuscitation should be kept available.

Although much has been written about oxygen toxicity, there appears to be little evidence of its clinical occurrence. Many of the reported instances of oxygen toxicity have been cases of irritation resulting from improperly humidified oxygen.

**Treatment of Hypoxia Associated With  $\text{CO}_2$  Retention.**

A Tracheostomy is usually necessary to reduce dead space and permit removal of secretions by catheter. The mechanical respirator (see below) should be attached directly to the tracheostomy tube if possible. The tracheostomy tube must be closed while the respirator is being operated by mouth.

B Oxygen may be administered by means of an automatic mechanical pressure device. This is the more effective method of removing  $\text{CO}_2$  rapidly because it promotes adequate ventilation.

C If high concentrations are not needed immediately, start with reduced concentrations and increase slowly as  $\text{CO}_2$  is removed.

**OXYGEN AT ATMOSPHERIC PRESSURE**

Oxygen is most commonly administered at atmospheric pressure.

Note Proper humidification must be maintained if necessary with aerosolized water or saline solution.

**Oxygen Tent.**

The transparent plastic tent is preferable because it permits the patient to see out. It must be inspected for tears before filling. Tuck edges securely under mattress to prevent leakage.

A, Advantages Gives moderate concentrations of oxygen at maximum comfort to the patient, and can be used with restless and uncooperative patients.

B Disadvantages Most expensive to buy and to operate, and cannot deliver high concentrations of oxygen. If not operated properly, oxygen concentration may fall and  $\text{CO}_2$  is likely to accumulate.

**Common Methods of  
Administering Oxygen at Atmospheric  
Pressure (Adults)**

Method	Usual Oxygen Concentrations	Usual Rate of Oxygen Flow (L./minute)
Tent	40-50%	Initiate at 15-30 Maintain at 12-15
Catheter*		
Nasopharyngeal (metal or rubber)	20-40%	6-8
Oropharyngeal	30-40%	6-8
Mask		
BLB or equivalent	80-100%	8-10
Expendable plastic masks	40-60%	10-15
OEM or Bennett face mask	80-100%	6-8

\*Very inefficient but generally the most useful of the several methods available

#### Nasal Catheter

This apparatus consists of a urethral catheter (French No. 10 or 12) with 4-6 small holes in the terminal inch, a reduction valve mechanism, and a humidifier bottle. A bilateral plastic or metal cannula which extends about one-half inch into the nares is also available.

The catheter should be cleaned, lubricated with petrolatum (but not mineral oil) and replaced every 6-12 hours. It may be placed in the nasopharynx or 1-2 inches into the nares but the concentrations achieved are usually only about 25-30%. For concentrations up to 40%, place the catheter in the oropharynx (or use a binasal catheter). To calculate the approximate distance the tube must be inserted into the oropharynx, measure the distance from the external nares to the tip of one earlobe, using the tube to measure with. Then pass the tube through the nose into the oropharynx. When the patient begins to swallow, withdraw the tube about one-half inch and secure it in place.

**A. Advantages** The nasal catheter is the least expensive method of administering oxygen and is more comfortable than a mask.

**B. Disadvantages** Very high concentrations of oxygen are not obtainable, and the mucosa may dry unless a humidifier is used.

#### Masks.

Several types of mask are available. The BLB mask is a nasal or oronasal rubber mask

with a rebreathing bag. The disadvantage of this mask is that with low oxygen flow (under 6-8 L./minute), CO<sub>2</sub> tends to accumulate. A flat rebreathing bag may also interfere with inspiration. Expendable plastic masks require a high oxygen flow but only low oxygen concentrations are achieved. OEM and Bennett face masks are similar to the BLB mask but do not permit rebreathing into the bag. A flutter type valve is used which prevents rebreathing of CO<sub>2</sub>.

**A. Advantages** Masks (except for the plastic masks) give the highest concentrations of oxygen obtainable without the use of pressure. The OEM and the Bennett masks have injector settings so that the oxygen concentration can be varied from 50 to 100%.

**B. Disadvantages** Tight masks cannot be tolerated by some patients.

### OXYGEN UNDER INCREASED PRESSURE

Various pressure breathing devices have been developed which allow oxygen to be administered under slight positive pressure during the inspiratory phase. Although these devices were originally employed for resuscitation (usually with a negative pressure phase in expiration), the value of intermittent positive pressure in the treatment of various acute and chronic pulmonary and cardiac disorders was soon recognized.

The principal physiologic effects of oxygen administered by pressure methods are as follows: (1) It helps overcome resistance to gas flow and widens the bronchioles, permitting more efficient cough and bronchial drainage. (2) It increases intrapulmonary mixing, creating more uniform alveolar aeration. (3) It decreases CO<sub>2</sub> return. (4) It inhibits fluid extravasation into the alveoli (hence is of value in pulmonary edema). (5) It interferes with venous return to the right heart, with consequent decrease in cardiac output and blood supply to the lungs. This is of value in the management of congestive failure, especially with associated pulmonary edema, in shock, on the other hand, it is a disadvantage, and the use of positive pressure devices is often contraindicated in shock for this reason.

#### Intermittent Positive Pressure Therapy Units.

The Bennett and the Bird units are 2 of the most efficient of the available pressure breathing devices. They may be used with an inter-



mittent nebulizer or with a Mist-O<sub>2</sub> Gen<sup>®</sup> continuous nebulizer for good humidification (or for administration of various antibiotics, vasodilators, and surface tension lowering agents). They are particularly useful in the administration of aerosols for they force the particles down into the terminal bronchioles and alveoli. Automatic cycling devices are available with both units. Clinical indications and uses are as follows

(1) Bronchial asthma - Useful mainly in the acute attack, especially with a bronchial dilator.

(2) Chronic emphysema, idiopathic or accompanying fibrosis, pneumoconiosis, and similar disorders - Apparently the best results are achieved when bronchial dilators are used. Use cautiously or with an automatic cycling device in patients with severe hypoxia and elevated CO<sub>2</sub> tension in these conditions therapy must be employed for 15-20 minutes each hour or even continuously until hypoventilation is corrected. For ambulatory treatment of emphysema, 2-4 treatments daily for 20 minutes each may be used. This may be continued as long as benefits are obtained. Treatment is given in courses of 5-30 days, which may be repeated as indicated.

(3) Bronchiectasis - As for chronic emphysema (see above). Antibiotics by aerosol are often useful.

(4) Pulmonary edema - Especially useful when associated with severe anoxia. Use with great caution if shock (forward failure) is present.

(5) Irritating gases and fumes - Very valuable, especially with associated pulmonary edema. Use until the lungs have cleared.

(6) Atelectasis - See p. 152.

(7) Respiratory depression - Must be used with caution if circulatory failure is also present.

(8) Right heart failure - Helps correct hypoxia and relieves the burden on the right heart. Excellent with other measures in management of acute right heart failure.

## ARTIFICIAL RESPIRATION

Although failure of ventilation may be corrected with a pressure breathing device applied to the airway, such a device is not always readily available and in any case cannot be employed for long periods. In such cases respiration can be maintained by applying mouth-to-mouth breathing or pressure variations to the chest wall or diaphragm. This maintains

normal intrapleural and atmospheric pressure relationships.

## NONMECHANICAL ARTIFICIAL RESPIRATION

Artificial respiration must be administered promptly to a person whose respirations have ceased, whether as a result of drowning, suffocation, electric shock, or other cause. Note: Artificial respiration should not be postponed while waiting for equipment.

Artificial respiration replaces spontaneous respiration and provides oxygen for tissue metabolism until the paralyzed respiratory center resumes its normal function. As long as the heart continues to beat the patient has a chance of recovery even after many hours of artificial respiration (See p. 208 for cardiac resuscitation).

Mouth-to-mouth breathing is more effective in most instances than the manual methods in producing a greater tidal exchange with relatively less effort and this method should be used if at all possible. A clear airway is essential, a pharyngeal airway should be used if available. The patient's nose must be closed while mouth pressure is being applied. Pressure sufficient to move the chest wall slightly is all that is necessary. High pressures should be avoided. The patient's exhalation is passive.

The "push-pull" methods are the most effective of the manual methods and are twice as effective as the simple push methods (e.g., Schafer).

### General Procedure.

Clear the airway and begin artificial respiration at once, a delay of only 1-2 minutes greatly reduces the victim's chances of recovery. Do not discontinue artificial respiration until normal respiration is established or until rigor mortis is unequivocal.

### Technic of Mouth-to-Mouth Breathing (See Diagram.)

**A. Position of Patient** If possible the patient is placed face up, lying on his back, although in an emergency this method can be applied in any position where the mouth is accessible.

**B. Position of Operator** The operator kneels at the side or above the head (when using a pharyngeal airway). Hold the mandible forward. The patient's nose is occluded and the patient's lips must be held closed around an airway.



**Method A:** Clear mouth and throat. Place patient supine. Insert left thumb between patient's teeth, grasp mandible firmly in midline, and draw it forward (upward) so that the lower teeth are leading. Close patient's nose with right hand. Gauze (as shown) or airway may be used but is not necessary.



**Method B:** Clear mouth and throat. Place patient supine. Pull strongly forward at angle of mandible. Close patient's nose with your cheek. Gauze (as shown) or airway may be used but is not necessary.



1 Place hands for arm-lift



2 Rock backward and lift arms



3 Place hands for back-pressure



4 Rock forward and press back

**Technics of Artificial Respiration.** Above: Mouth-to-mouth resuscitation (preferred method). Left: Arm-lift, back-pressure (Nielsen) method.

**C. Procedure** The operator blows into the patient's mouth (or airway) with sufficient force to elevate the anterior chest. Much less force must be used for children and infants than for adults. After several rapid breaths to establish oxygenation in the starved tissues, the rate should be slowed to 10-12 breaths per minute.

#### Technic of the Arm-Lift, Back-Pressure Method (Nielsen).

A. Positions of Patient and Operator (See diagram )

B. The Rate of Resuscitation The rate of resuscitation is maintained at 10-12 complete cycles per minute. This rate can be timed by a watch, or by counting in the following manner 1001, 1002, 1003, 1004, 1005, and then repeating. Each number requires about 1 second, so that the numbers thus counted represent a five-second cycle. Three seconds should be allowed for each arm lift, and 2 for the back pressure. When possible, operators should be alternated at intervals of 20-60 minutes.

#### C. Procedure of Resuscitation

1. Arm-lift - The arms of the operator are kept straight during the entire procedure. The operator lifts the patient's arms upward and toward himself as he rocks backward on his knees. This enlarges the thoracic cage and causes inspiration. The arm lift is continued until resistance is met the patient's arms are then returned to the ground and the operator places the palms of his hands on the patient's back.

2. Back-pressure - With the palms of the hands on the lower part of the shoulder blades and the fingers extended over the thoracic cage, the operator rocks forward on his knees and with his arms straight exerts strong pressure directly downward on the thorax until resistance is met.

3. The cycle is then repeated.

#### MECHANICAL RESUSCITATORS

In competent hands, mechanical resuscitators are more effective than manual artificial respiration and should be used as soon as available at the site of emergency. It should be emphasized that a mechanical resuscitator should be used only by trained personnel and when it is in proper operating condition.

#### AEROSOL THERAPY

There are 2 types of aerosol therapy *intermittent and continuous*. Intermittent therapy is the more commonly used, although continuous administration of water or saline solution by mists of fine particle size probably permits better humidification, with less irritation from oxygen, and appears to be more physiologic than steam inhalations. Continuous aerosol should probably be employed where there is actual or potential tracheobronchial irritation. Antibiotics and bronchial dilators may be used by this method.

The administration of antibiotic agents by aerosol inhalation has been of value in some lung infections

#### Equipment.

A Nebulizer The nebulizer used for aerosol therapy must produce particles smaller than 8-10  $\mu$  in diameter. The most satisfactory nebulizers are the Vaponephrine<sup>®</sup> model and the De Vilbiss No 40<sup>®</sup>. For continuous administration of aerosols, apparatuses with larger capacities are available (e.g., Mist-O<sub>2</sub>-Gen<sup>®</sup>, Humidox<sup>®</sup>)

B Sources of Pressure for Nebulizing Drug Oxygen from a cylinder at 6-10 L./minute is most commonly used. Compressed air from a diaphragm-type compressor may be used (Caution Do not use an oil-sealed pump )

#### Drugs & Concentrations Employed

All solutions should be prepared fresh daily. The frequency and duration of treatment depends upon the disease and its severity

#### A Antibiotics

- 1 Penicillin - The usual dose is 50-100 thousand units/treatment Dilute in 1-2 ml. of water.
- 2 Streptomycin - 0.25-0.5 Gm. in 1-2 ml of water.
- 3 Oxytetracycline (Terramycin<sup>®</sup>) aerosol - 50-100 mg in 1-2 ml. of 75% propylene glycol.

B Enzymes: Pancreatic dornase (Dornase<sup>®</sup>) is sometimes effective in dissolving thick tenacious mucus or dead tissue in chronic bronchitis or bronchiectasis. Some irritation of the pharynx and tracheobronchial membranes may occur, and excessive secretions after treatment sometimes cause difficulty. The recommended dose is 50-100 thousand units 1-4 times daily aerosolized in the special diluent provided by the manufacturer.

## C Bronchial Dilators

1 Isoproterenol hydrochloride (Isuprel<sup>®</sup>, Aludrine<sup>®</sup>), 0.1-0.5 ml of 1:100, 1:200, or 1:400 solution

2 Epinephrine, 0.5 ml of 1:100 solution

D Surface Tension Lowering Agents Various surface tension lowering agents (e.g., Superfnone<sup>®</sup>, Alevaire<sup>®</sup>, ethyl alcohol) have been advocated for liquefying tenacious secretions

## Methods of Administration.

For the greatest effect and efficiency the aerosol should be inhaled through the mouth. Nebulization with an intermittent positive pres-

sure device (Bennett valve) is a very efficient method. For continuous pressure from an oxygen tank a 'Y' tube is inserted between the nebulizer and the source of pressure. Nebulization will occur only when the unattached end of the tube is closed with the thumb or a finger; there is usually a few seconds' delay before the aerosol arrives at the mouth piece. Intermittent pressure (e.g., using a foot bellows or hand bulb pump) is applied during inspiration.

If the patient is unable to cooperate, the nebulizer may be used with an oxygen mask which has a rebreathing bag. The nebulizer is placed between the mask and the oxygen source.

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## Heart & Great Vessels

Maurice Sokolow & Henry Brainerd

The complete diagnosis of any cardiovascular disease consists of (1) determining the etiology, (2) identifying the structural changes, (3) defining the physiologic abnormalities, and (4) assessing the remaining functional capacity of the heart. Treatment and the estimation of prognosis are both based upon a clear understanding of these 4 factors.

Etiology is established by considering the patient's age, the history, the specific abnormalities present, and appropriate laboratory studies, such as antistreptolysin O titer, serologic test for syphilis, and protein-bound iodine. Abnormalities of cardiac structure and function are identified by careful physical examination combined with radiologic and electrocardiographic studies. In congenital (and occasionally in acquired) heart disease, cardiac catheterization is needed to determine the extent of shunts and to measure the pressures in the heart chambers, aorta, or pulmonary artery. Dye-dilution tests are useful in some otherwise undetectable right-to-left or left-to-right shunts. Angiocardiography may be needed to outline transposition of the vessels, pulmonary arteriovenous fistula, and the site and extent of coarctation or aneurysm of the aorta.

### NONSPECIFIC MANIFESTATIONS

The most common symptoms resulting from heart disease are dyspnea, fatigue, chest pain, and palpitation. However, because any of these symptoms may be due to noncardiac disorders (even in patients with known heart disease), the proper interpretation of their significance depends upon systematic inquiry and diagnostic studies.

#### Dyspnea.

The most common type of dyspnea due to heart disease is exertional dyspnea - distinct shortness of breath upon moderate exertion which is relieved by rest.

Orthopnea is dyspnea in recumbency which is promptly relieved by sitting up. It occurs only in advanced stages of heart failure.

Paroxysmal nocturnal dyspnea suddenly awakes the patient and forces him to sit on the side of the bed or stand up for relief. It may be the first symptom of left ventricular failure or tight mitral stenosis. Dyspnea due to heart disease is almost always associated with cardiac enlargement and other structural or physiologic changes.

Noncardiac causes of exertional dyspnea include poor physical condition, obesity, debility, advanced age, chronic lung disease, anemia, and obstruction of the nasal passages. Orthopnea occurs in extreme obesity, tense ascites due to any cause, abdominal distention due to gastrointestinal disease, and in the third trimester of pregnancy. Paroxysmal nocturnal dyspnea can be simulated by bronchial asthma appearing in adult life for the first time and by airway obstruction due to paratracheal tumors.

Anxiety states and cardiac neuroses can produce any form of dyspnea, but such patients often describe sighing respirations and complain of inability to take in a satisfying breath. Psychogenic dyspnea is also associated with acute respiratory alkalosis, which causes light-headedness or mental clouding, paresthesias of the limbs or around the mouth, and at times frank tetany, tremulousness, and apprehension.

#### Fatigue.

Easy fatigability which is relieved by rest is common in low-output states and heart failure. It may be the chief complaint (rather than dyspnea) in congenital heart disease, or pulmonary, or mitral stenosis complicated by pulmonary hypertension. Asthenia - continual exhaustion and lethargy which are not improved by rest - is due to such psychologic disorders as depression, cardiac neuroses, and chronic anxiety, or may be a component of effort syndrome ("neurocirculatory asthenia"). Noncardiac organic causes of fatigue include chronic infections, anemia, endocrine and metabolic disorders, chronic poisoning, habitual use of

depressant or sedative drugs, malignancy, collagen diseases, and any debilitating illness.

### Chest Pain.

Chest pain occurs in the following cardiovascular disorders: Angina pectoris (in which the pain is due to intermittent ischemia of the myocardium), myocardial infarction, myopericarditis, pericardial effusion or tamponade, aortic dissection or aneurysm, and pulmonary embolism or infarction.

Chest pain is one of the most common presenting complaints in medicine. Careful evaluation includes inquiry concerning its quality, location, radiation, duration, and the factors which precipitate, aggravate, or relieve it. Serial examinations are often required, as well as laboratory tests. Exercise tests and therapeutic tests are seldom necessary.

The following noncardiac disorders are often associated with chest pain which resembles or is indistinguishable from that of heart disease: (1) Arthritis or disk disease of the lower cervical and upper thoracic spine (dorsal or ventral nerve root pain), (2) Cardiac neurosis, (3) Neurocirculatory asthenia, (4) Sliding hiatus hernia, acute or chronic cholecystitis, acute pancreatitis, cardiospasm, peptic ulcer, esophageal pain, (5) Disorders causing local chest wall pain, e.g., costochondritis, strain or inflammation of the pectoral and intercostal muscles and ligaments, postmyocardial infarction syndrome, (6) Periarthritis of the left shoulder, (7) Spontaneous pneumothorax, (8) Pleurisy, spinal cord disease, mediastinal tumor, neoplastic invasion of ribs or vertebrae, (9) Mediastinal emphysema.

### Palpitation.

Consciousness of rapid, forceful or irregular beating is the most common complaint referable to the heart. In the vast majority of instances palpitation is due to increased awareness of normal heart action either because of anxiety about the presence of heart disease or secondary to long-standing emotional disorders such as neurocirculatory asthenia. Organic causes are anemia, thyrotoxicosis, debility, and paroxysmal arrhythmias.

Two types of palpitation are most often described. Sinus tachycardia, a rapid, forceful pounding which may begin gradually or suddenly but invariably slows gradually, occurs normally on exertion or during excitement. Premature ventricular systoles cause a sensation of the heart "skipping a beat" or "stopping and turning over."

Patients with true paroxysmal tachycardia describe a rapid, regular palpitation or "flut-

tering" sensation which begins suddenly, lasts minutes or hours, and then ceases abruptly. In younger patients there are no other symptoms unless the attacks are prolonged. In older patients paroxysmal arrhythmias may produce angina pectoris, congestive heart failure or syncope. Paroxysmal atrial fibrillation is felt as a rapid irregular pounding which begins and ends suddenly. Chronic atrial fibrillation and flutter are in themselves usually not perceived by the patient except after exercise or excitement when the ventricular rate increases.

An electrocardiogram taken during an episode of palpitation establishes the diagnosis. However, clinical observation of the heart rate and rhythm and the effect of exercise and carotid sinus pressure, together with an assessment of the over-all clinical picture (age of the patient, associated heart and other diseases) permits accurate diagnosis in the great majority of cases without electrocardiograms.

## SIGNS OF HEART DISEASE

Valuable information pertaining to the etiology, nature, and extent of heart disease is often found on general physical examination, e.g., Argyll Robertson pupils, splinter hemorrhages, splenomegaly, diffuse goiter, large kidneys, congenital anomalies, or epigastric bruit. Abnormal pulsations of the neck veins or precordium, cyanosis, clubbing, and edema should be carefully noted. Careful palpation may disclose right or left ventricular hypertrophy, thrills, and diastolic shocks.

### Edema.

Edema caused by heart failure appears first in the ankles and lower legs of ambulatory patients and over the sacrum, buttocks, and posterior thighs of bedridden patients.

The mere presence of edema does not establish a diagnosis of heart failure in a patient who also complains of dyspnea. Significant edema occurs often in obese patients and those with incompetent leg veins and healed thrombophlebitis. Garters, rolled or elastic-top stockings, tight girdles, prolonged sitting or standing, premenstrual fluid retention, and "idiopathic edema of women" are other common noncardiac causes. Nephrosis or terminal nephritis, cirrhosis with tense ascites, congenital or acquired lymphedema, idiopathic hypoproteinemia, severe malnutrition or anemia, and obstruction of the inferior vena cava can produce dependent edema.

### Cyanosis.

Cyanosis is classified as central or peripheral. Central cyanosis results from low arterial oxygen saturation caused by intracardiac right-to-left shunts, pulmonary arteriovenous fistula, certain chronic lung diseases, or lobar pneumonia. It is differentiated from peripheral cyanosis by being present also on warm mucous membranes such as the insides of the lips and cheeks and on the tongue and conjunctivas. Polycythemia vera may produce central cyanosis despite normal oxygen saturation since the larger numbers of red cells produce a proportionately greater increase in the amount of reduced hemoglobin. A useful means of differentiating cyanosis caused by a shunt in the heart or lung from that caused by primary lung disease is to administer 100% oxygen cyanosis caused by shunt will be unaffected, whereas that due to parenchymal lung disease will disappear.

Peripheral cyanosis occurs in the presence of normal arterial oxygen saturation. It only occurs on cool portions of the body, such as the fingertips, nose, ears, and cheeks. It is caused by slowed circulation through peripheral vascular beds, which allow the capillary blood to give up more than normal amounts of oxygen. Reduced cardiac output due to mitral stenosis, pulmonary stenosis, or heart failure causes peripheral cyanosis, but the most common causes are nervous tension with cold, clammy hands, and exposure to cold.

### Murmurs.

Auscultation permits the examiner to determine the presence of structural or functional abnormalities by noting changes in the first or second heart sounds, the appearance of additional heart sounds or extracardiac sounds, and by analysis of murmurs. The examiner must also recognize the sounds which have no known pathologic significance: normally split first sound, mid-systolic click, normal third sound, cardiorespiratory murmurs, and the innocent heart murmurs. Accurate interpretation of murmurs is difficult in the presence of gross heart failure with very low cardiac output or rapid ventricular rates. In these situations restoration of compensation or slowing of the ventricular rate may cause prominent murmurs to decrease in intensity; previously faint or inaudible murmurs may in turn become loud.

**A. Systolic Murmurs:** A soft short systolic murmur at any valve area may be innocent if there are no other abnormalities and if it changes markedly with respiration and position. Exercise and tachycardia increase the intensity of any murmur. This so-called innocent or functional systolic murmur is usually

present at the mitral or pulmonary area and is most easily heard in recumbent, thin-chested individuals; full inspiration causes it to disappear or diminish markedly, whereas full expiration may accentuate it considerably. The louder a systolic murmur, the more likely it is to be organic in origin. Time is the only sure way of differentiating innocent and organic murmurs. Any systolic murmur associated with a thrill at that valve area is due to valvular disease unless there is gross anemia. An apical pansystolic murmur which merges with and replaces the first sound and which is well transmitted into the left axilla or left infra-scapular area is organic, i.e., is due to deformity of the mitral valve or dilatation of the mitral valve ring with regurgitation. An aortic systolic murmur is "ejection" in type and mid-systolic. It is transmitted into the carotids or upper interscapular area when due to organic disease of the aortic valve or to dilatation of the base of the aorta. This murmur is often heard well at the apex of the heart.

**B Diastolic Murmurs** Diastolic murmurs may result from dilatation of the heart (acute myocarditis, severe anemia), dilatation of the aortic ring (marked hypertension), deformity of a valve, or intracardiac shunts. When listening for diastolic murmurs, attention should be focussed only on diastole, excluding from awareness as far as possible the first heart sound and any systolic murmurs.

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## FUNCTIONAL & THERAPEUTIC CLASSIFICATION OF HEART DISEASE\*

**Functional Capacity. (Four classes.)**

**Class I:** No limitation of physical activity.

Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

**Class II:** Slight limitation of physical activity. Comfortable at rest, but ordinary

\*Criteria Committee, New York Heart Association.

physical activity results in fatigue, palpitation, dyspnea, or anginal pain

**Class III:** Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain

**Class IV:** Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency, or of the anginal syndrome, may be present even at rest if any physical activity is undertaken, discomfort is increased

#### Therapeutic Classification. (Five classes)

**Class A:** Physical activity need not be restricted, but unusually severe or competitive efforts should be avoided

**Class B:** Ordinary physical activity need not be restricted, but unusually severe or competitive efforts should be avoided

**Class C:** Ordinary physical activity should be moderately restricted, and more strenuous efforts should be discontinued

**Class D:** Ordinary physical activity should be markedly restricted

**Class E:** Should be at complete rest, confined to bed or chair

## CONGENITAL HEART DISEASES

Congenital lesions account for about 2% of all heart disease in adults.

The following classification and relative frequency of defects is based on a study by Paul Wood

#### Classification.

##### A. Without Shunt

1 Right-sided - Pulmonary stenosis (12%)

2 Left-sided - Coarctation of aorta (9%)  
aortic stenosis (3%).

##### B With Shunt

##### 1 Acyanotic -

Atrial septal defect (20%)

Patent ductus arteriosus (13%)

Ventricular septal defect (9%)

##### 2. Cyanotic -

Tetralogy of Fallot (11%)

Pulmonary stenosis with reversed intratracheal shunt (3%)

Eisenmenger's syndrome (3%).

Tricuspid atresia (1.5%).

Other congenital anomalies, involving the skeletal system especially, are present in an estimated 20% of cases.

#### Pathogenesis of Clinical Manifestations

Congenital heart disease produces symptoms and signs by one or more of the following mechanisms

**A. Stenosis of a Valve or Vessel (A, (above))** Causing hypertrophy of the proximal ventricle and eventual heart failure with the usual manifestations.

**B Left-to-right Shunt (B.1, above)** Shunting of blood from the left atrium or ventricle to the right atrium or ventricle increases the work of the right ventricle and the amount of pulmonary blood flow at the expense of systemic flow. In large shunts, and in smaller ones during exercise, this discrepancy is exaggerated, and dyspnea and fatigue occur. For unknown reasons, some of these shunts cause pulmonary hypertension, reversal of shunt occurs converting the original left-to-right shunt into a right-to-left shunt (Eisenmenger's syndrome) Hemoptysis may occur.

**C Right-to-left Shunt (B.2, above)** Shunting of "venous" blood from the right atrium or ventricle into the aorta, left atrium or left ventricle, bypassing the pulmonary circulation, causes arterial unsaturation which beyond a certain point is recognizable clinically as cyanosis. Squatting may bring relief of exertional dyspnea and fatigue. Syncope occurs when pulmonary blood flow is very low. Compensatory polycythemia results from the persistent unsaturation, and this in turn may be responsible for cerebral thrombosis in severe cases. Clubbing usually accompanies gross cyanosis.

In addition to the specific hemodynamic effects of the lesions themselves, metastatic bacterial abscesses in a bacterial endocarditis may develop, especially in ventricular septal defect, patent ductus arteriosus, and bicuspid aortic valve. In addition to x-ray and ECG study, cardiac catheterization, angiocardiology, or dye-dilution curves are often necessary to delineate accurately the nature and magnitude of existing defects.

#### Differential Diagnosis

**A. Auscultatory Signs** A history of a murmur present in infancy, congenital anomalies elsewhere in the body, and the finding of murmurs and thrills in areas separate from those of valve lesions found in rheumatic heart disease are helpful. A thrill and murmur along the left sternal border is most often due to con-



genital heart disease, although aortic stenosis may confuse the diagnosis. Soft to prominent apical mid-diastolic murmurs are present in septal defect and patent ductus arteriosus but none of the other characteristics of mitral stenosis are present. Venous hum over the upper parasternal area may be confused with the continuous murmur of patent ductus arteriosus or aortic-pulmonary communication, but it is abolished or markedly diminished by recumbency.

**B. Cyanosis With Clubbing** Cyanosis, clubbing, and polycythemia may also occur in chronic cor pulmonale secondary to lung disease, and in congenital pulmonary arteriovenous fistula. When there is serious question regarding the origin of cyanosis and clubbing, response of arterial oxygen to inhalation of 100% oxygen is helpful, because the arterial oxygen saturation cannot rise to normal if a shunt is present.

**C. Cyanosis Without Clubbing** Cyanosis without clubbing and polycythemia is usually "peripheral," secondary to reduced cardiac output, or slowed peripheral circulation. Arterial oxygen saturation is normal.

If after careful study potentially remediable congenital heart disease remains a diagnostic possibility, the patient should be referred for cardiac catheterization, angiocardiology, and dye indicator studies.

## PURE PULMONARY STENOSIS

Stenosis of the pulmonary valve or infundibulum increases the resistance to outflow, raises the right ventricular pressure, and limits the amount of pulmonary blood flow. Since there is no shunt, arterial saturation is normal, but severe stenosis causes peripheral cyanosis by reducing cardiac output. Clubbing or polycythemia never develops unless a patent foramen ovale is present, permitting shunting of blood from the right to the left atrium.

### Clinical Findings.

**A. Symptoms and Signs:** Mild cases are asymptomatic. Moderate to severe stenosis causes dyspnea on exertion (in the absence of heart failure), fainting, and chest pain. Right ventricular failure develops eventually in severe cases, producing edema, increased dyspnea, and fatigue.

There is a palpable right ventricular heave. A loud, harsh systolic murmur and a prominent thrill are heard in the left second and third interspaces parasternally, the murmur is in the third and fourth interspaces in infundibular stenosis. The second sound is obscured by the murmur in severe cases, the pulmonic component is diminished and widely split from  $A_2$  or absent. Both components are audible in mild cases. A presystolic gallop and a prominent "a" wave in the venous pulse are present in severe cases.

**C X-ray findings and Fluoroscopy:** The heart size may be normal, or there may be a prominent right ventricle and atrium or gross cardiac enlargement, depending upon the severity. The pulmonary artery is dilated with weak or absent pulsations in valvular stenosis, normal in infundibular stenosis. Pulmonary vascularity is normal or (in severe cases) diminished.

**D Electrocardiographic Findings** Right axis or right ventricular hypertrophy, peaked P waves.

**E Special Studies** Cardiac catheterization permits estimation of the gradient across the pulmonic valve, determines whether the stenosis is valvular or infundibular, and, together with dye studies, demonstrates the presence or absence of associated shunts.

### Treatment.

Pure pulmonic stenosis with evidence of progressive hypertrophy and resting gradients over 80 mm Hg is treated surgically with low operative mortality and excellent results in most cases. All lesions are corrected under direct vision; some gradients can be obliterated by valvotomy through the pulmonary artery with brief inflow occlusion. Since most lesions have associated outflow tract hypertrophy, the majority are now approached through a ventriculotomy with extracorporeal circulation.

### Prognosis.

Patients with mild stenosis may have a normal life expectancy unless bacterial endocarditis occurs. Severe stenosis causes refractory heart failure in the twenties and thirties.

Blount, S.G., Jr., Vigoda, P.S., & H. Swan: Isolated infundibular stenosis. *Am Heart J.* 57:684-700, 1959.

Campbell, M.: Indications for and results of surgical treatment of congenital heart disease. *Advances Int. Med.* 10:81-105, 1960.

## COARCTATION OF THE AORTA

The adult type of coarctation of the aorta consists of localized narrowing of the aortic arch just distal to the origin of the left subclavian artery in the region of the ligamentum arteriosum. A bicuspid aortic valve is present in 25% of cases. BP is elevated in the aorta and its branches proximal to the coarctation and decreased distally. Collateral circulation between the high and low pressure aortic segments develops through the intercostal arteries and branches of the subclavian arteries.

### Clinical Findings

**A Symptoms and Signs** There are no symptoms until the hypertension produces left ventricular failure or cerebral hemorrhage. Strong arterial pulsations are seen in the neck and suprasternal notch. Hypertension is present in the arms but the pressure is normal or low in the legs. This difference is exaggerated by exercise, which is helpful in the diagnosis of doubtful cases. Femoral pulsations are absent or weak and delayed in comparison with the brachial pulse. Visible or palpable collateral arteries are present in the intercostal spaces and along the borders of the scapulas. Late systolic ejection murmurs at the base are often heard better posteriorly especially over the spinous processes.

**B X-ray Findings** X-ray shows scalloping of the ribs due to enlarged collateral intercostal arteries; dilatation of the left subclavian artery and poststenotic aortic dilatation ( '3' sign), and left ventricular enlargement.

**C ECG Findings** The ECG shows left ventricular hypertrophy. It may be normal in mild cases.

### Treatment

Resection of the coarcted site is a more formidable operative procedure than ligation of a patent ductus arteriosus and the surgical mortality is in the neighborhood of 3% even in the best hands. For this reason not all physicians recommend routine resection in asymptomatic patients. The risks of the disease are such however that if a skilled heart surgeon is available all coarctations in patients up to the age of 20 years should be resected. In patients between the ages of 20 and 35 surgery is advisable if the patient is doing badly. The mortality rises considerably in patients over 50 years of age and surgery in this age group is of doubtful value.

### Prognosis

Most patients with the adult form of coarctation die before the age of 40 from the complications of hypertension: rupture of the aorta, bacterial endocarditis, or cerebral hemorrhage (congenital aneurysms). However 25% of patients have a normal cardiovascular prognosis and die of causes unrelated to the coarctation.

Gross, R. E. Coarctation of the aorta. *Circulation* 7: 757-68, 1953.

Reifenstein, G. H., Levine, S. A., & R. E.

Gross. Coarctation of the aorta: a review of 104 autopsied cases of the "adult type" 2 years of age or older. *Am Heart J* 33: 146-68, 1947.

## ATRIAL SEPTAL DEFECT

The most common form of atrial septal defect is persistence of the ostium secundum in the mid-septum; less commonly the ostium primum persists, involving the endocardial cushion in which case mitral or tricuspid abnormalities may also be present. In both instances normally oxygenated blood from the left atrium passes into the right atrium, increasing the right ventricular output and the pulmonary blood flow. In the primum defect mitral valve insufficiency produces additionally strain on the left ventricle.

### Clinical Findings

**A Symptoms and Signs** Most patients are asymptomatic. With large shunts exertional dyspnea occurs. Prominent right ventricular pulsations are readily visible and palpable. A moderately loud systolic murmur can be heard in the second and third interspaces parasternally and an apical or xiphoid mid-diastolic soft murmur. Thrills are uncommon. The second sound is widely split and this does not vary with respiration.

**B X-ray Findings** Large pulmonary arteries with vigorous pulsations, increased pulmonary vascularity, an enlarged right atrium and ventricle, and a small aortic knob.

**C ECG Findings** Right axis or right ventricular hypertrophy is always present. Incomplete or complete right bundle branch block is present in most cases, and left axis deviation in ostium primum defect.

**D Special Studies** Cardiac catheterization permits calculation of the amount of blood shunted. The catheter may pass through the defect into the left atrium.

#### Treatment

Minor degrees of atrial septal defect do not require surgery. Surgery should be withheld from patients with pulmonary hypertension with reversed shunt because of the risk of acute right heart failure. Lesions with a large left to right shunt (more than 2 or 3 times systemic flow) without increased pulmonary arterial resistance should be operated upon. The surgical risks now are sufficiently low so that patients with a pulmonary to systemic flow rate of 1.5:1 should probably be operated upon. Closure of the defect is preferably done with cardiac catheterization.

#### Prognosis

Most patients with small shunts survive to middle or late life before pulmonary hypertension or heart failure appear. Large shunts cause disability and death by age 40.

Bedford, D E, & T H Sellors. Atrial septal defect. In *Modern Trends in Cardiology* (edited by A Morgan Jones). Hoeber, 1961.

Dexter, L. Atrial septal defect. *Brit Heart J* 18:209-25, 1956.

### PATENT DUCTUS ARTERIOSUS

The embryonic ductus arteriosus fails to close normally and persists as a shunt connecting the left pulmonary artery and aorta usually near the origin of the left subclavian artery. Blood flows from the aorta through the ductus into the pulmonary artery continuously in systole and diastole. It is a form of arteriovenous fistula. Increasing the work of the left ventricle in some patients obliterative changes in the pulmonary vessels cause pulmonary hypertension. Then the shunt is bidirectional or right to left.

#### Clinical Findings

**A Symptoms and Signs** There are no symptoms until left ventricular failure develops. The heart is of normal size or slightly enlarged with a forceful apex beat. Pulse pressure is wide and diastolic pressure is low. A continuous 'rough machinery' murmur accentuated in late systole, is heard best in the left first and second interspaces at the sternal

border. Thrills are common. Paradoxical splitting of the second sound may be present if there is considerable left ventricular hypertrophy.

**B X ray Findings** The heart is normal in size and contour, or there may be left ventricular and left atrial enlargement. The pulmonary artery, aorta, and left atrium are prominent.

**C ECG Findings** Normal pattern or left ventricular hypertrophy.

**D Special Studies** Cardiac catheterization establishes the presence of a left to right shunt and the catheter may be passed through the ductus into the aorta from the pulmonary artery.

#### Treatment

The indications for ligation or division of a patent ductus arteriosus in the presence of pulmonary hypertension have not been established. Current opinion favors ligation whenever the flow through the ductus is permanently or intermittently from left to right, i.e., when pulmonary blood flow is increased.

Because of the low operative mortality rate (less than 1%) in skilled hands, division and closure is recommended in both children and adults. The mortality rate becomes higher as the patient becomes older. This necessitates caution in recommending surgery in older adults who are asymptomatic and have no left ventricular hypertrophy. Subacute bacterial endocarditis is the major hazard in this group.

#### Prognosis

Large shunts cause a high mortality early in life. Smaller shunts are compatible with long survival. Congestive heart failure being the most common complication. Bacterial endocarditis may also occur. A small percentage of patients develop pulmonary hypertension and reversal of shunt such that the lower legs especially the toes appear cyanotic in contrast to normally pink fingers. At this stage the patient is inoperable.

Gross, R E, & L A Longino. The patent ductus arteriosus: observations from 412 surgically treated cases. *Circulation* 3:125-37, 1951.

Lukas, D S, Araujo, J, & I Steinburg. The syndrome of patent ductus arteriosus with reversal of flow. *Am J Med* 17:298-310, 1954.

Cardiac Catheterization Data\*

	Pressure (mm. Hg)			Percentage Oxygen Saturation				Significant Findings on Catheterization
	RA	RV	PA	VC	RA	RV	PA	A
Normal values	1-5/0-2	20-30/0-4	20-30/8-12	85-75	65-75	65-75	65-75	85-90
Atrial septal defect	Normal	Normal or sl. incr	Normal or sl. incr	Normal	> VC	Same as RA	Same as RA	Catheter passes from RA to LA
Ventricular septal defect	Normal or high	Normal or high	Normal or high	Normal	Normal	> RA	Same as RV	Catheter passes into LV and aorta
Patent ductus arteriosus	Normal or high	Normal or high	Normal or high	Normal	Normal	Normal	> RV	Catheter passes from PA into aorta
Pulmonary stenosis	Normal or high	High	Normal or low	Normal	Normal	Normal	Normal	Significant gradient of pressure across pulmonic valve.
Tetralogy of Fallot	Normal or high	High	Normal or low	Low	Same as VC	Same as VC	Same as VC	Catheter passes from RV into aorta, gradient across pulmonic valve.
Eisenmenger's syndrome	Normal or high	High	High	Low	Same as VC	Same as VC	Same as VC	Catheter passes into LV or aorta from RV, no gradient across pulmonic valve.

VC = vena cava

RA = right atrium

LA = left atrium

RV = right ventricle

PA = pulmonary artery

A = peripheral artery

&gt; = greater than

\*Modified from T.G. Schnabel, Jr., &amp; others, Pennsylvania M J 57 363, 1954 The most significant findings are in bold type

## VENTRICULAR SEPTAL DEFECT

In this lesion a persistent opening in the upper interventricular septum due to failure of fusion with the aortic septum permits blood to pass from the high-pressure left ventricle into the low-pressure right ventricle. In one-fourth to one-third of cases the shunt is not large enough to strain the heart. With large shunts, both left and right ventricular strain may develop.

### Clinical Findings.

**A. Symptoms and Signs** Large shunts cause dyspnea on exertion. A long, loud, harsh systolic murmur and thrill are found in the left third and fourth interspaces along the sternum. The heart is otherwise "normal." In large shunts right ventricular contraction is palpable and there is a separate forceful apical impulse, a mid-diastolic "flow murmur," and a third heart sound heard at the apex.

**B. X-ray Findings:** With large shunts the right or left ventricle (or both), the left atrium, and the pulmonary arteries are enlarged, and pulmonary vascularity is increased.

**C. ECG Findings:** May be normal or may show right, left, or biventricular hypertrophy.

**D. Special Studies:** Cardiac catheterization permits a definitive diagnosis in all but the most trivial defects.

### Treatment.

Ventricular septal defects vary in severity from trivial asymptomatic lesions with normal cardiac hemodynamics to extensive lesions causing death from cardiac failure in infancy. The former do not require surgery. The ideal case for curative repair with cardiac by-pass technique is one with a large left-to-right shunt, left ventricular hypertrophy, and no more than moderate pulmonary hypertension. When severe pulmonary hypertension is present (pulmonary arterial pressures of more than 85 mm Hg) and the left-to-right shunt is small, the surgical mortality risk is about 50%. If the shunt is reversed, surgery is contraindicated.

### Prognosis.

Patients with the typical murmur as the only abnormality have a normal life expectancy except for the threat of bacterial endocarditis. With large shunts, congestive heart failure may develop early in life and survival beyond age 40 is unusual. Shunt reversal occurs in an

estimated 25%, producing Eisenmenger's syndrome.

Blount, S.G., Mueller, H., & J.C. McCord: Ventricular septal defect. Clinical and hemodynamic patterns. *Am.J.Med.* 18:871-82, 1955

Dammann, J.F., Jr., Sosa, O., & I. Christlieb: Anatomy, physiology, and natural history of simple ventricular septal defects. *Am.J.Cardiol.* 5:136-66, 1960.

## TETRALOGY OF FALLOT

Pulmonary stenosis together with a high interventricular septal defect, which allow the right ventricle to empty into the aorta, prevent venous blood from passing normally into the pulmonary artery. Instead, blood passes from the right ventricle into the aorta and into the left ventricle. Aortic blood is therefore markedly unsaturated, and cyanosis, polycythemia, and clubbing appear early. Exercise causes cyanosis to deepen.

### Clinical Findings.

**A. Symptoms and Signs** Development is retarded in severe cases. Dyspnea is common, squatting relieves fatigue and dyspnea, and syncope occasionally occurs. Prominent signs are cyanosis and clubbing, a slight right ventricular heave and absent apical impulse, and a short, harsh systolic murmur and thrill along the left sternal border. The heart is not enlarged. A single loud second sound is heard unless the lesion is mild, when the second sound is split with the pulmonary component decreased in amplitude.

**B. X-ray Findings:** The lung fields are abnormally clear. The apex of the heart is blunted, with a concavity in the pulmonary artery segment (boot-shaped heart). A right aortic arch is present in 25% of cases.

**C. ECG Findings** The tracing may show right axis deviation to frank right ventricular hypertrophy. Prominent P waves are occasionally present.

**D. Special Studies** Cardiac catheterization and angiocardiology together establish the diagnosis.

### Treatment.

Tetralogy of Fallot is treated surgically using extracorporeal circulation, and the

operative mortality rate is reasonably low. Patients with underdeveloped pulmonary arteries and those weighing less than 15 Kg. should be given a preliminary Bialock shunt if severe oxygen deprivation (as indicated by cyanosis) threatens survival.

### Prognosis

Tetralogy is the commonest cause of cyanotic congenital heart disease in adults, but even so survival to adult life is not common. Severe hypoxemia is the commonest cause of death. Vascular thromboses secondary to polycythemia are also common.

Keith, J D., Rowe, R D., & P Vlad: *Heart Disease in Infancy and Childhood* Macmillan, 1958

McCord, M C., Van Elk, J., & S G. Blount: *Tetralogy of Fallot. Clinical and hemodynamic spectrum of combined pulmonary stenosis and ventricular septal defect.* *Circulation* 16 736-44, 1957

## PULMONARY STENOSIS WITH REVERSED INTERATRIAL SHUNT

The elevated pressure in the right ventricle causes right ventricular hypertrophy and decreased distensibility. Venous blood therefore passes more readily from the right atrium through the atrial defect into the left atrium. Arterial unsaturation results, and may be sufficient to produce all the consequences of 'cyanotic congenital heart disease'.

### Clinical Findings.

A. Symptoms and Signs. Exertional dyspnea and fatigue, cyanosis, clubbing and polycythemia, a long, harsh pulmonic systolic murmur and thrill, and slight to prominent right ventricular pulsation.

B. X-ray Findings: Slight to moderate cardiac enlargement, decreased pulmonary vascularity, and a dilated pulmonary artery (in valvular stenosis).

C. ECG Findings. Right ventricular hypertrophy and prominent P waves.

D. Special Studies. Cardiac catheterization and angiocardiology are helpful in distinguishing this lesion from tetralogy.

### Treatment.

Correction of pulmonic stenosis decreases right ventricular pressure and permits the atrial

shunt to again become left to right if it is not closed. The shunt is usually corrected at the same operation.

### Prognosis.

Survival beyond early adult life is rare.

Espino-Vela, Jr., & E. Piccolo: *Pulmonary stenosis. In: Congenital Heart Disease* (edited by D.P. Morse). Davis, 1962  
Wood, P.: *Diseases of the Heart and Circulation*, 2nd ed. Lippincott, 1956

## EISENMENGER'S SYNDROME

This lesion was originally defined as ventricular septal defect, right ventricular hypertrophy, and over-riding of the aorta, producing cyanosis, but it is now thought of as pulmonary hypertension causing reversal of any originally left-to-right shunt. In order of frequency the defects most commonly resulting in this mechanism of shunt reversal are ventricular septal defect, patent ductus arteriosus, and atrial septal defect (rare under age 21 or in secundum defects). The cause of the pulmonary hypertension is not known, in many cases it may have been present from birth. The increased pulmonary resistance causes right ventricular hypertrophy, and variable shunt reversal occurs. Blood still passes from left to right as well as from right to left.

### Clinical Findings.

A. Symptoms and Signs. Moderate to severe exertional dyspnea is common. Ventricular septal defect and atrial septal defect cause cyanosis with clubbing and polycythemia. Reversed ductus causes cyanosis of the lower legs and toes. Right ventricular and pulmonary artery pulsations are palpable, and a systolic murmur can be heard along the left sternal border.

B. X-ray Findings. Large, actively pulsating central pulmonary arteries with reduced peripheral pulmonary vascularity are noted on fluoroscopy.

C. ECG Findings. Right ventricular hypertrophy with peaked P waves is the usual finding.

D. Special Studies. Cardiac catheterization, angiocardiology, and dye dilution studies may be necessary to establish the cause.

### Treatment.

No surgical treatment is effective in Eisenmenger's syndrome.

### Prognosis.

Most patients die of heart failure, vascular thrombosis, or endocarditis before 30 years of age.

DuShane, J. W., & J. W. Kirklin: Selection for surgery of patients with ventricular septal defect and pulmonary hypertension. *Circulation* 21:13-27, 1960.

Wood, P.: The Eisenmenger syndrome. *Brit M J.* 2:701-9 and 755-62, 1958

## TRICUSPID ATRESIA

Atresia of the tricuspid valve may occur (1) as an isolated lesion, (2) with stenosis of the pulmonary arteries together with atrial septal defect, or (3) in association with ventricular septal defect or patent ductus arteriosus. Blood from the right atrium passes into the left atrium and reaches the lungs by passing through a ventricular septal defect into the right ventricle or, when the right ventricle and the pulmonary artery are rudimentary, by shunting from the aorta into the pulmonary circulation through a patent ductus.

Examination reveals a strong apical impulse, a systolic murmur and thrill along the left sternal border, cyanosis, clubbing, and polycythemia. The ECG reveals left axis deviation or left ventricular hypertrophy. Angiocardiology and cardiac catheterization are necessary for definitive diagnosis. Anastomosis of the subclavian artery to the pulmonary artery (Blalock) is probably the procedure of choice if the pulmonary blood flow is low. The benefits of anastomosis of the right atrium to the pulmonary artery have not yet been established.

The prognosis for life is poor. Only an occasional patient survives to adulthood.

Brown, J. W., & others: Tricuspid atresia

*Brit. Heart J.* 18:499-518, 1956.

Campbell, M.: Tricuspid atresia and its prognosis with and without surgical treatment.

*Brit. Heart J.* 23:699-710, 1961.

## ACQUIRED VALVULAR DISEASES

### RHEUMATIC FEVER

#### Criteria for Diagnosis (Modified After Jones).

##### A. Major Criteria

1. Carditis.
2. Sydenham's chorea.
3. Fascial nodules.
4. Erythema marginatum.
5. Polyarthritides.

##### B. Minor Criteria

1. Fever
2. Polyarthralgia.
3. Prolongation of P-R interval.
4. Increased sedimentation rate or C-reactive protein.
5. Evidence of antecedent beta-hemolytic streptococcus infection
6. Verified history of previous rheumatic fever or presence of rheumatic valvular disease.

The diagnosis of rheumatic fever is almost certain when 2 or more major criteria are present. Nevertheless, rheumatoid arthritis, neurocirculatory asthenia, bacterial endocarditis, collagen diseases, and chronic infectious disease can reproduce the early manifestations of rheumatic fever.

#### General Considerations.

Rheumatic fever is a subacute or chronic systemic disease which for unknown reasons may either be self-limiting or may lead to slowly progressive valvular deformity. Rarely, it is acute and fulminant.

Rheumatic fever is the commonest cause of heart disease in people under 50 years of age. In over-all incidence, it ranks third behind hypertension and atherosclerotic coronary disease. It is somewhat more common in males than in females, but chorea is seen more frequently in females. The peak incidence occurs between the ages of 5 and 15, rheumatic fever is rare before the age of 4 and after 50.

Rheumatic fever is initiated by an infection with group A hemolytic streptococci, appearing usually 1-4 weeks after tonsillitis, nasopharyngitis, or otitis.

The acute phase of rheumatic fever may involve the endocardium, myocardium, pericardium, synovial joint linings, lungs, or pleura. The characteristic lesion is a perivascular granulomatous reaction and vasculitis. The mitral valve is attacked in 75-80% of cases, the aortic valve in 30%, the tricuspid and pul-

monary valve in less than 5%. Small pink granules appear on the surface of the edematous valve. Healing may be complete, or a progressive scarring due to subacute or chronic inflammation may develop over months and years.

## Clinical Findings.

### A. Major Criteria

1 Carditis - The presence of carditis establishes the diagnosis of rheumatic fever whenever there is (1) a definite history of rheumatic fever, or (2) valvular disease clearly of rheumatic origin or (3) whenever a streptococcal infection of the upper respiratory tract is known to have occurred within the preceding 4 weeks. Carditis is most apt to be evident in children and adolescents, in adults it is often best detected by serial ECG study. Any of the following establishes the presence of carditis

(1) Pericarditis - Either fibrinous (with a pleuritic type of precordial, epigastric, or left shoulder pain, friction rub, characteristic ST-T changes on the ECG) or with effusion of any degree. It is uncommon in adults and is at times diagnosed by the progressive increase in "heart shadow" on serial chest x-rays

(2) Cardiac enlargement, detected by physical signs or x-ray, indicating dilatation of a weakened, inflamed myocardium. Serial x-rays are often needed to detect the change in size

(3) Frank congestive failure - right- and left-sided. Right heart failure is more prominent in children, and painful engorgement of the liver is a valuable sign.

(4) Mitral or aortic diastolic murmurs, indicative of dilatation of a valve ring or the myocardium with or without associated valvulitis

In the absence of any of the above definite signs the diagnosis of carditis depends upon the following less specific abnormalities considered in relation to the total clinical picture

(1) ECG changes - P-R prolongation greater than 0.04 sec above the patient's normal is the most significant abnormality, changing contour of P waves or inversion of T waves is less specific

(2) Changing quality of heart sounds

(3) Pansystolic apical murmur which persists or becomes louder during the course of the disease and is transmitted into the axilla. The Carey Coombs short mid-diastolic murmur should be carefully sought

(4) Gallop rhythm - Difficult to differentiate from the physiologic third sound in children and adolescents

(5) Sinus tachycardia out of proportion to the degree of fever, persisting during sleep and markedly increased by slight activity.

(6) Arrhythmias, shifting pacemaker, ectopic beats.

2 The 2 following signs occur most often in association with severe carditis and so are of little value in initial diagnosis, occasionally, however, they appear before carditis is evident and constitute strong presumptive evidence of rheumatic fever.

(1) Erythema marginatum (annulare) - Frequently associated with skin nodules. The lesions begin as rapidly enlarging macules which assume the shape of rings or crescents with clear centers. They may be slightly raised and confluent. The rash may be surprisingly transient or may persist for long periods.

(2) Subcutaneous nodules - These are uncommon except in children. The nodules may be few or many, are usually small (2 cm. or less in diameter) firm, nontender, and are attached to fascia or tendon sheaths over bony prominences such as the elbows, the dorsal surfaces of the hands, the malleoli, the vertebral spines, and the occiput. They persist for varying periods, are usually recurrent, and are clinically indistinguishable from the nodules of rheumatoid arthritis.

3 Sydenham's chorea may appear suddenly as an isolated entity with no "minor criteria" or may develop in the course of overt rheumatic fever. Eventually 50% of cases have other signs of rheumatic fever. Girls are more frequently affected, and occurrence in adults is rare. Chorea consists of continual, nonrepetitive, purposeless jerky movements of the limbs, trunk, and facial muscles. Milder forms masquerade as undue restlessness as the patient attempts to convert uncontrolled movements into seemingly purposeful movements. Facial grimaces of infinite variety are common. These movements are made worse by emotional tension and disappear entirely during sleep. The episode lasts several weeks occasionally months.

4 Arthritis - The arthritis of rheumatic fever is characteristically a migratory polyarthritis of gradual or sudden onset which involves the large joints sequentially, one becoming hot, red, swollen, and tender as the inflammation in the previously involved joint subsides. The body temperature rises progressively as each successive joint becomes inflamed. In adults only a single or a small joint may be affected. The acute arthritis lasts 1-5 weeks and subsides without residual deformity. Note: Joint involvement is considered a major criterion only when definite effusion and signs of inflammation are present. This is in contrast to arthralgia, in which pain or stiffness is present without these objective signs. Prompt response of arthritis to therapeutic doses of salicylates is characteristic (but not diagnostic) of rheumatic fever.



With respect to arthritis, the dictum, "One major and 2 minor criteria," is a source of diagnostic confusion. Arthritis and arthralgia are common in children and young adults, often accompanied by fever and an increased sedimentation rate. Streptococcal infection or "sore throat" is also common. Coincidental association of these factors thus often leads to an unwarranted diagnosis of rheumatic fever. A definite diagnosis requires bona fide evidence of carditis or the appearance of additional rheumatic manifestations such as erythema marginatum or chorea.

B. The following common nonspecific manifestations are of diagnostic help only when associated with other more specific features

1. Fever is always present with arthritis and carditis. In subacute or chronic phases it is low-grade and may be continuous or intermittent. Fever is important only as evidence of an inflammatory process. Children and even adults may have normal peak temperatures of 37.5-37.8°C. (99.5-100°F.), and this should not be construed erroneously as "fever."

2. Malaise, asthenia, weight loss, and anorexia may be the only overt effects of a smoldering rheumatic state, but are also characteristic of any chronic active disease.

3. Abdominal pain is common. It is variable in site and severity and occasionally leads to an unnecessary laparotomy. It may result from liver engorgement, sterile rheumatic peritonitis, or rheumatic enteritis, or may be referred from the pleura or pericardium.

4. Recurrent epistaxis is believed by some clinicians to be a sign of "subclinical" rheumatic fever.

5. "Growing pains" in joints, periarticular tissues, or muscle insertions may be a symptom of rheumatic fever ("arthralgia")

C Laboratory Findings These are helpful in 3 ways

1. As nonspecific evidence of inflammatory disease - Sedimentation rate and C-reactive protein are almost always increased during active rheumatic fever except when chorea is the only clinical sign. Variable leukocytosis and normochromic anemia may appear. Slight proteinuria and microhematuria are occasionally seen and may not indicate concomitant glomerulonephritis

2. As evidence of antecedent beta-hemolytic streptococcal infection - A high titer or increasing antistreptolysin O titer indicates recent infection but does not mean that rheumatic fever is present. Throat culture is positive for beta-hemolytic streptococci in 50% of cases of active rheumatic fever.

3. As strong evidence against the diagnosis - A low antistreptolysin O titer (50 Todd

units) which does not rise on repeated tests tends to rule out rheumatic fever. A normal sedimentation rate is rare in the presence of active rheumatic fever

### Complications

Congestive heart failure occurs in severe cases. Other complications include cardiac arrhythmias, pericarditis with large effusion, rheumatic pneumonitis, pulmonary embolism and infarction, cardiac invalidism, and early or late development of permanent heart valve deformity

### Differential Diagnosis.

Rheumatic fever may be confused with the following: Rheumatoid arthritis, osteomyelitis, traumatic joint disease, neurocirculatory asthenia or cardiac neurosis, bacterial endocarditis, pulmonary tuberculosis, chronic meningococcemia, acute poliomyelitis, disseminated lupus erythematosus, serum sickness, drug sensitivity, leukemia, sickle cell anemia, inactive rheumatic heart disease, congenital heart disease, and "surgical abdomen"

### Prevention of Recurrent Rheumatic Fever.

The principles of prevention are to avoid beta-hemolytic streptococcal infections if possible and to treat streptococcal infections promptly and intensively with anti-infective drugs.

A. General Measures Avoid contact with persons who have "colds" or other upper respiratory infections. Patients with rheumatic fever should live in an equable climate, where streptococcal infections are less common

B Prevention of Infection Two methods of prevention are now advocated

1. Penicillin 200-250 thousand units orally every day before breakfast, or benzathine penicillin G (Bicillin®), one million units I.M. once a month. This is advocated especially for children who have had one or more acute attacks and should be given throughout the school year. Adults should receive preventive therapy for about 5 years after an attack. It is most important to give preventive penicillin between September and June.

2. Sulfonamides - If the patient is sensitive to penicillin, give sulfadiazine or sulfisoxazole (Gantrisin®) 0.5-1 Gm. (7½-15 gr.) daily throughout the year. Caution: Patients receiving sulfonamides should have periodic blood counts and urinalyses. If there is any tendency toward leukopenia, the drug should be stopped immediately.

C Treatment of Streptococcal Sore Throat It has been shown that prompt therapy (within

24 hours) of streptococcal infections with 600-900 thousand units of benzathine penicillin G (Bicillin®) I.M. or 300-600 thousand units of procaine penicillin with aluminum monostearate in oil (PAM®) I.M. every third day for 3 injections (or equivalent) will prevent most attacks of acute rheumatic fever.

#### Treatment.

##### A Medical Treatment

1. Salicylates - The salicylates markedly reduce fever and relieve joint pain and may reduce joint swelling. There is no evidence that they have any effect on the natural course of the disease. Note: The salicylates should be continued as long as necessary to relieve pain, swelling, or fever. If withdrawal results in a recurrence of symptoms, treatment should immediately be reinstituted.

(1) Sodium salicylate is the most widely used of this group of drugs. Give 1-2 Gm (15-30 gr) every 2-4 hours orally in sufficient doses to allay symptoms and fever. In an occasional patient maximum doses may not be completely effective. There is no evidence that I.V. administration has any advantage over the oral route. Early toxic reactions to the salicylates include tinnitus, nausea, and vomiting. Sodium salicylate may be given in enteric-coated 0.5 Gm. (7½ gr) pills or with equal doses of sodium bicarbonate to reduce gastric irritation. Caution: Never use sodium salicylate or sodium bicarbonate in patients with acute rheumatic fever who have associated cardiac failure.

(2) Acetylsalicylic acid may be substituted for sodium salicylate, with the same dosages and precautions.

(3) Aminopyrine (Pyramidon®) 0.2-0.4 Gm (3-6 gr) every 3-4 hours, may be used if the salicylates are not tolerated. Check the WBC every 2-4 days when giving this drug.

2. Penicillin should be employed in the treatment as well as the prevention of rheumatic fever to reduce the incidence of long-term sequelae. See p. 657 for intensive penicillin therapy schedules.

3. Corticotropin (ACTH) and the cortisones - Although remarkable results have been observed in certain patients with acute rheumatic fever who have been treated with these drugs, the improvement is often only temporary. There may be a prompt disappearance of fever, malaise, tachycardia, and polyarthritides. Abnormal ECG changes (prolonged P-R interval) and sedimentation rates may return to normal limits within a week. If corticotropin or corticosteroids are to be employed, most investigators feel that they should be used within 3 weeks after the onset of carditis. Optimal

dosage schedules have not been established and it is not known what influence the drugs may have on the development of subsequent cardiac lesions.

A suggested schedule, to be started as soon as rheumatic fever is diagnosed or strongly suspected, is as follows: Give prednisone, 5-10 mg orally every 6 hours for 3 weeks, and then gradually withdraw over a period of 3 weeks by reducing and then discontinuing first the nighttime, then the evening, and finally the daytime doses. In severe cases the dosage should be increased, if necessary, to levels adequate to control symptoms (see the discussion of the dangers and precautions in the use of corticosteroids in Chapter 17).

B General Measures - Bed rest should be enforced until all signs of active rheumatic fever have disappeared. The criteria for this are as follows: Return of the temperature to normal with the patient at bed rest and without medications; normal sedimentation rate; normal resting pulse rate (under 100 in adults); return of ECG to normal or fixation of abnormalities. The patient may then be allowed up slowly, but several months should elapse before return to full activity unless the rheumatic fever was exceedingly mild. Maintain good nutrition.

##### C Treatment of Complications

1. Congestive failure - Treat as for congestive failure (see p. 216), with the following variations:

(1) A low-sodium diet and diuretics are of particular value in promoting diuresis and treating failure in acute rheumatic fever.

(2) Digitalis is usually not as effective in acute rheumatic fever as in most cases of congestive failure and may accentuate the myocardial irritability, producing arrhythmias which further embarrass the heart. Digitalis should be given, but with extreme care.

(3) Many cases of congestive failure are due to acute myocarditis. These often respond dramatically to corticotropin (ACTH) or the cortisones. When sodium-retaining hormonal agents are employed, rigorous sodium restriction (under 200 mg. daily) or thiazide drugs are imperative.

2. Pericarditis - Treat as any acute non-purulent pericarditis. The rheumatic effusion is sterile, and antibiotics are of no value. The general principles include relief of pain, by opiates if necessary, and removal of fluid by cardiac paracentesis if tamponade develops. This, however, is rarely necessary. If paracentesis is performed it should be preceded and followed by a short course of penicillin.

therapy to prevent contamination of the pericardium. Corticotropin (ACTH) and the cortisones as well as salicylates should be continued or started, as they seem to have a specific favorable effect in aiding resorption of the fluid.

### Prognosis.

Initial episodes of rheumatic fever last months in children and weeks in adults. Twenty per cent of children have recurrences within 5 years. Recurrences are uncommon after 5 years of well-being, and rare after the age of 21. The immediate mortality is 1-2%. Persistent rheumatic activity with a greatly enlarged heart, heart failure, and pericarditis indicate a poor prognosis, 30% of children thus affected die within 10 years of the initial attack. Otherwise the prognosis for life is good. Eighty per cent of all patients attain adult life, and half of these have little if any limitation of activity. Approximately one-third of young patients have detectable valvular damage after the initial episode, most commonly a combination of mitral stenosis and insufficiency. After 10 years, two-thirds of surviving patients will have detectable valvular disease. In adults, residual heart damage occurs in less than 20% and is generally less severe. Mitral insufficiency is the commonest residual, and aortic insufficiency is much more common than in children. The influence of steroids on prognosis is as yet not known. Twenty per cent of patients who have chorea develop valvular deformity even after a long latent period of apparent well being.

**Jones Criteria (Modified) for Guidance in the Diagnosis of Rheumatic Fever:** Report of The Committee on Standards and Criteria for Programs of Care, *Circulation* 18:617-20, 1958.

Wannamaker, L.W., & E.M. Ayoub: Antibody titers in acute rheumatic fever *Circulation* 21:598-614, 1960.

### RHEUMATIC HEART DISEASE (Rheumatic Valvulitis, Inactive)

Chronic rheumatic heart disease results from single or repeated attacks of rheumatic fever which produce rigidity and deformity of the cusps, fusion of the commissures, or shortening and fusion of the chordae tendinae. Stenosis or insufficiency results and both often co-exist, although one or the other predominates. The mitral valve alone is affected in 50-60% of

cases, combined lesions of the aortic and mitral valves occur in 20%, pure aortic lesions in 10%. Tricuspid involvement occurs only in association with mitral or aortic disease in about 10% of cases. The pulmonary valve is rarely affected.

### Clinical Findings.

A history of rheumatic fever is obtainable in only 60% of patients with rheumatic heart disease.

The earliest evidence of organic valvular disease is a significant murmur. The earliest evidence of hemodynamically significant valvular lesions is found on x-ray, fluoroscopy, and ECG study, since these will reveal the earliest stages of specific chamber enlargement. Careful inspection and palpation also permit accurate diagnosis of advanced valve lesions.

The important findings in each of the major valve lesions are summarized in the tables on pp 184 and 185. Hemodynamic changes, symptoms, associated findings, and course are discussed below.

### Management of Asymptomatic Valvular Heart Disease.

#### A. Prevention

1 Recurrences of acute rheumatic fever can be prevented by (1) avoiding exposure to streptococcal infections, (2) continuous antibiotic prophylaxis in selected patients under 35 and those who have been exposed to known hemolytic streptococcal infections, and (3) prompt and adequate treatment of infections with hemolytic streptococci.

2. The patient should be given advice in regard to dental extraction, urologic procedures, surgical procedures etc., to prevent bacteremia and possible subacute bacterial endocarditis.

B. General Measures Vocational guidance is necessary to anticipate possible reduced exercise tolerance in later life. Follow-up observations should emphasize early recognition of disturbances of thyroid function, anemia, and arrhythmias, maintenance of general health, and avoidance of obesity and excessive physical exertion.

### 1. MITRAL STENOSIS

Over 75% of patients with mitral stenosis are women below the age of 45. Relatively slight degrees of narrowing are sufficient to

Differential Diagnosis of Rheumatic Heart Disease

	Mitral Stenosis	Mitral Insufficiency	Aortic Stenosis	Aortic Insufficiency	Tricuspid Stenosis	Tricuspid Insufficiency
Inspection	Malar flush Precordial bulge and diffuse pulsation in young patients	Usually forceful apical impulse to left of MCL	Localized heaving PMI Carotid pulsations weak exhibiting slow rise	Generalized pallor Strong abrupt carotid pulsations Forceful PMI to left of MCL and down Capillary pulsations	Glant a wave in jugular pulse with sinus rhythm Often slate colored skin (mixed jaundice and local cyanosis)	Large V wave in jugular pulse
Palpation	Tapping sensation over area of expected PMI Mid diastolic and/or presystolic thrill at apex Small pulse Right ventricular pulsation left 3rd 5th ICS parasternal when pulmonary hypertension is present	Forceful brisk PMI systolic thrill over PMI Pulse normal small or slightly collapsing	Powerful heaving localized PMI to left of MCL and slightly down Systolic thrill over aortic area (best felt with patient leaning forward breath held in maximum expiration) Plateau pulse small and slowly rising	Apical impulse forceful and displaced significantly to left and down Water hammer pulse	Mid diastolic thrill between lower left sternal border and PMI Presystolic pulsation of liver (sinus rhythm only)	Right ventricular tricuspid pulsation Occasionally systolic thrill at lower left sternal edge Systolic pulsation of liver
Percussion	Dullness in left 3rd ICS parasternally ACD normal or slightly enlarged to left only	ACD increased to left of MCL and slightly down	ACD slightly enlarged to left and down	Definite cardiac enlargement to left and down		Usually cardiac enlargement to left and right
Heart sounds rhythm and BP	Loud snapping M1 Opening snap along left sternal border or at apex Atrial fibrillation common BP normal	M1 normal or buried in murmur 3rd heart sound Delayed opening snap occasionally present Atrial fibrillation common BP normal	A2 normal or delayed and weak may be absent BP normal or systolic pressure normal with high diastolic level Ejection click occasionally present just preceding murmur	Sounds normal or A2 loud Wide pulse pressure with diastolic pressure < 60 mm Hg	M1 often loud	Atrial fibrillation usually present

Murmurs	Location and transmission	Sharply localized at or near apex. Graham Steel murmur along left sternal border in severe pulmonary hypertension.	Lowest over PMI, transmitted to left axilla, left infrascapular area.	Right 2nd ICS parasternal and/or at apex, heard in carotids and occasionally in upper interscapular area.	Lowest along left sternal border in 3rd-4th interspace. Also heard over aortic area and apex.	3rd-5th ICS along left sternal border out to apex.	As for tricuspid stenosis.
Timing	Onset at opening snap ("mid-diastolic") with presystolic accentuation if in sinus rhythm. Mid-diastolic only in atrial fibrillation. Graham Steel begins with A <sub>2</sub> .	Onset at opening snap ("mid-diastolic") with presystolic accentuation if in sinus rhythm. Mid-diastolic only in atrial fibrillation. Graham Steel begins with A <sub>2</sub> .	Pansystolic. begins with M1 and ends at or after A <sub>2</sub> .	Mid-systolic: begins after M1, ends before A <sub>2</sub> , reaches maximum intensity in mid-systole.	Begins immediately after aortic 2nd sound and ends before 1st sound.	As for mitral stenosis.	As for mitral insufficiency.
Character	Low-pitched, rumbling, presystolic murmur merges with loud M1 in a "crescendo" pitch, blowing.	Low-pitched, rumbling, presystolic murmur merges with loud M1 in a "crescendo" pitch, blowing.	Blowing, high-pitched, occasionally harsh or musical.	Harsh, rough.	Blowing, often faint.	As for mitral stenosis.	Blowing, coarse, or musical.
Optimum auscultatory conditions	After exercise, left lateral recumbency. Bell chest piece lightly applied.	After exercise, left lateral recumbency. Bell chest piece lightly applied.	After exercise, diaphragm chest piece.	Patient resting, leaning forward, breath held in full expiration. Bell chest piece, lightly applied.	Slow heart rate, patient leaning forward, breath held in expiration. Diaphragm chest piece.	Murmur usually louder during and at peak of inspiration. Patient recumbent. Bell chest piece.	Murmur usually becomes louder during inspiration.
X-ray and fluoroscopy	Straight left heart border, large left atrium sharply indenting esophagus. Large right ventricle and pulmonary artery if pulmonary hypertension present.	Straight left heart border, large left atrium sharply indenting esophagus. Large right ventricle and pulmonary artery if pulmonary hypertension present.	Enlarged left ventricle and left atrium, systolic expansion of left atrium if enlargement not extreme.	Concentric left ventricular hypertrophy. Prominent ascending aorta, small knob. Calcified valve common.	Moderate to great left ventricular hypertrophy. Prominent aortic knob. Strong aortic pulsation on fluoroscopy.	Enlarged right atrium only.	Enlarged right atrium and ventricle.
ECG	Broad P waves in standard leads, broad negative phase of diphasic P in V <sub>1</sub> . Normal axis. If pulmonary hypertension is present, tall peaked P waves, right axis deviation or right ventricular hypertrophy appears.	Broad P waves in standard leads, broad negative phase of diphasic P in V <sub>1</sub> . Normal axis. If pulmonary hypertension is present, tall peaked P waves, right axis deviation or right ventricular hypertrophy appears.	Left axis deviation or frank left ventricular hypertrophy. P waves broad, tall, or notched in standard leads, broad negative phase of diphasic P in V <sub>1</sub> .	Left ventricular hypertrophy.	Left ventricular hypertrophy.	Wide tall peaked P waves. Normal axis.	Right axis usual.

produce the auscultatory signs. When the valve has narrowed to less than 1.5 cm patients experience dyspnea and fatigue whenever their heart rate increases. The short diastolic interval during tachycardia results in inadequate ventricular filling. Consequently, the cardiac output falls and blood accumulates in the atrium and the pulmonary veins and capillaries. Eventually pulmonary congestion is present continually and symptoms increase in severity. Recumbency at night further increases the pulmonary blood volume causing orthopnea, paroxysmal nocturnal dyspnea or actual transudation of fluid into the alveoli leading to acute pulmonary edema. Severe pulmonary congestion may also be initiated by acute bronchitis or any acute respiratory infection by development of subacute bacterial endocarditis or recurrence of acute rheumatic carditis. As a result of long-standing pulmonary venous hypertension anastomoses develop between the pulmonary and bronchial veins in the form of bronchial submucosal varices. These often rupture, producing mild or severe hemoptysis.

Fifty to 80% of patients develop paroxysmal or established atrial fibrillation which until controlled produces dyspnea or pulmonary edema. Twenty to 30% of these patients in turn will later have major emboli in the cerebral, visceral or peripheral arteries as a consequence of thrombus formation in the left atrium.

Right ventricular hypertrophy, dilatation and failure appear eventually in 40-50% of patients, producing the typical signs of right heart failure.

In a few patients for unknown reasons the pulmonary arterioles become narrowed or constricted, this greatly increases the pulmonary artery pressure and accelerates the development of right ventricular failure. These patients have relatively little dyspnea but experience great fatigue and weakness on exertion because of the markedly reduced cardiac output.

## Treatment

Mitral incompetence must be excluded if possible. The mitral valve is operable only if symptoms are due to a mechanical obstruction of the mitral valve, although replacement of the valve may increase the indications for surgery (see Mitral Insufficiency). If the signs of mitral stenosis are present but there is no systolic murmur, mitral incompetence is exceedingly unlikely. If there is a loud pansystolic murmur at the apex in association with an accentuated, often early third heart sound, a soft first sound, and no opening snap, the diagnosis of predominant mitral incompetence is likely even if a short mid-diastolic murmur

can be heard at the apex. Unless hypertension or an aortic valvular lesion is present, left ventricular hypertrophy shown on ECG should make one very cautious in recommending surgery for mitral stenosis because in this circumstance the mitral valve is probably incompetent. If there is a moderate systolic murmur at the apex, the diagnosis depends upon a consideration of the total findings.

Special diagnostic studies such as dye dilution and pressure curves from the left ventricle and left atrium during left heart catheterization or left ventricular puncture may prove helpful in difficult cases.

Because the course of mitral stenosis is highly variable and because of the high mortality and morbidity of mitral valvulotomy (3-5%) and the frequency of restenosis, surgery is not advised in mild cases with slight exertional dyspnea and fatigue only. Indications for surgery include the following: (1) Signs of mitral stenosis with a pliable valve (opening snap, snapping first sound). (2) Uncontrollable pulmonary edema. (3) Disabling dyspnea and occasionally pulmonary edema. (4) Evidence of active pulmonary hypertension with right ventricular hypertrophy and early congestive failure. (5) Systemic and pulmonary emboli. (6) Increased pulmonary arteriolar resistance with marked dyspnea and increased  $P_2$ . These patients are apt to develop right heart failure and emboli. (7) Right heart failure with atrial fibrillation, tricuspid incompetence when secondary to marked mitral stenosis. The diagnosis of mitral stenosis is difficult under these circumstances and the surgical mortality is higher.

- Likoff, W., & J. Uricchio. Results of mitral commissurotomy. Clinical status of two hundred patients five to eight years after operation. *J. A. M. A.* 166:737-40, 1958.
- Wood, T. An appreciation of mitral stenosis. *Brit. M. J.* 1:1051-63 and 1113:24, 1954.

## 2 MITRAL INSUFFICIENCY

During ventricular systole, the mitral leaflets do not close normally and blood is forced back into the atrium as well as through the aortic valve. The net effect is an increased work load in the left ventricle. The left atrium enlarges progressively, but the pressure in pulmonary veins and capillaries rises only transiently during exertion. Patients have exertional dyspnea and fatigue which usually pro-

gress slowly over many years. Left ventricular failure eventually develops, and orthopnea and paroxysmal dyspnea may appear, followed rapidly by the symptoms of right heart failure.

When heart failure is fully developed, the response to therapy is incomplete and the patient remains incapacitated. Mitral insufficiency, like stenosis, predisposes to atrial fibrillation, but this arrhythmia does not provoke acute pulmonary congestion, and fewer than 5% of patients have peripheral arterial emboli. Mitral insufficiency especially predisposes to subacute bacterial endocarditis.

#### Treatment.

If the disability is great enough to warrant the substantial surgical risk, pure mitral insufficiency is considered a surgical lesion to be approached under direct vision from the left side. Most lesions can be significantly improved with posterior annuloplasty or a plastic sponge buttress. Combined mitral stenosis and insufficiency must be clearly distinguished from pure mitral insufficiency, since these valves tend to be thickened, fixed, and calcific, and prosthetic replacement during cardiac bypass offers the only surgical hope for this lesion. These devices, now used only experimentally, are nearing practical reality.

Bentivoglio, L., Uricchio, J., & H. Goldberg: Clinical and hemodynamic features of advanced rheumatic mitral regurgitation. *Am. J. Med.* 30:372-81, 1961.

Kay, E. B., Nogueira, C., & H. A. Zimmerman: Correction of mitral insufficiency under direct vision. *Circulation* 21:568-77, 1960.

### 3. AORTIC STENOSIS

Over 80% of patients with aortic stenosis are men. Slight narrowing, roughened valves, or aortic dilatation may produce the typical murmur and thrill without causing significant hemodynamic effects. When the valve area is less than one-fifth of normal, ventricular systole becomes prolonged and the typical plateau pulse develops. At this stage exertional dyspnea, fatigue, and pounding of the heart are noted. Cardiac output is ultimately markedly reduced so that patients have angina pectoris, great weakness or giddiness on exertion, or syncope. Survival beyond 3 years is uncommon if any of these appear. Many patients develop myocardial infarction, and 30% or more die suddenly.

#### Treatment.

The indications for surgical correction of aortic stenosis are progressive left ventricular failure, attacks of syncope due to cerebral ischemia, and angina pectoris when it is thought to be due to the decreased cardiac output of aortic stenosis and not to associated coronary artery disease. In the presence of both mitral and aortic stenosis, surgical correction of both valves can be performed at the same procedure.

The technical features of the operation are being revised, and open heart surgery with extracorporeal circulation is now favored. The mortality rate is high, however, and the lesion must be severe before surgery can be recommended.

Kirklin, J. W., & H. T. Mankin: Open operation in the treatment of calcific aortic stenosis. *Circulation* 21:578-86, 1960.

Wood, P. Aortic stenosis. *Am. J. Cardiol.* 1:553-71, 1958.

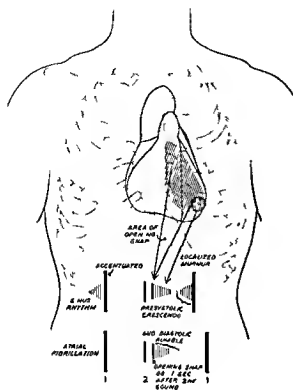
### 4. AORTIC INSUFFICIENCY

For many years the only sign may be a soft aortic diastolic murmur, i.e., "auscultatory" aortic insufficiency, indicating regurgitation of a very small amount of blood through the incompetent leaflets during diastole. As the valve deformity increases, larger and larger amounts regurgitate, diastolic BP falls, the pulse wave assumes its characteristic contour, and the left ventricle progressively enlarges. This is the stage of "dynamic" aortic insufficiency. Many patients remain asymptomatic even at this point, or experience exertional dyspnea. Left ventricular failure often begins abruptly with acute pulmonary edema or recurrent paroxysmal nocturnal dyspnea and orthopnea, fatigue, weakness, and exertional dyspnea are then incapacitating. Angina pectoris, or protracted chest pain simulating angina, appears in many. The heart failure is refractory to treatment and is the chief cause of death. Ten to 15% of these patients die suddenly.

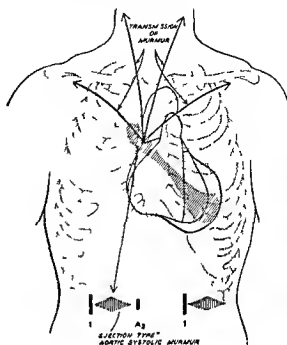
#### Treatment.

Aortic insufficiency is a surgically correctable lesion which sometimes requires only simple suturing or plication but often requires prosthetic replacement of a single cusp or the entire valve. Although these procedures are no longer experimental, the high surgical risk

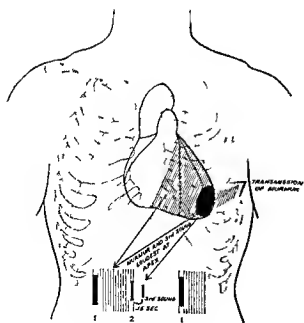
## MURMURS &amp; CARDIAC ENLARGEMENT IN COMMON VALVE LESIONS



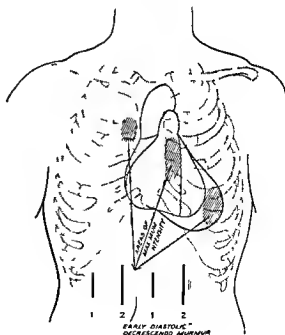
Mitral Stenosis



Aortic Stenosis



Mitral Insufficiency



Aortic Insufficiency



and the uncertain prognosis limit the indications to patients with class III lesions, and to clinical centers experienced in valve replacement.

Gorlin, R., & others: Dynamics of the circulation in aortic valvular disease. *Am.J.Med.* 18:855-70, 1955.

Segal, J., Hsrvey, P., & C. Hufnagel: A clinical study of 100 cases of severe aortic insufficiency. *Am.J.Med* 21:200-10, 1956

## 5. TRICUSPID STENOSIS

Most patients with tricuspid stenosis are women, and mitral valve disease is usually present also. Tricuspid stenosis acts as a mechanical block to the return of blood to the heart, and the systemic venous engorgement is analogous to the pulmonary venous engorgement caused by mitral stenosis. Tricuspid stenosis should be suspected when "right heart failure" appears early in the course of mitral disease, marked by hepatomegaly, ascites, and dependent edema. These are more prominent when atrial fibrillation is present. Severe fatigue is usual. Cardiac cirrhosis develops early, and patients acquire a characteristic complexion which is a blend of peripheral cyanosis and slight jaundice. Careful examination is needed to differentiate the typical diastolic rumble along the lower left sternal border from the murmur of mitral stenosis. In the presence of sinus rhythm, a presystolic liver pulsation can be found in half of the patients, in atrial fibrillation only the slow emptying of the jugular vein during diastole is noted. A giant right atrium on a chest film or angiogram confirms the diagnosis of tricuspid valve disease.

### Treatment.

Congenital tricuspid stenosis is associated with an underdeveloped right ventricle and does not lend itself to valvotomy. Diversion of the superior vena caval flow into the right lung is a relatively safe closed procedure which confers a significant degree of palliation.

Acquired tricuspid stenosis is extremely rare, and may be amenable to valvotomy under direct vision.

Killip, T., III, & D.S. Lukas: Tricuspid stenosis: physiologic criteria for diagnosis and hemodynamic abnormalities. *Circulation* 16:3-13, 1957.

Perloff, J.K., & W.P. Harvey: Clinical recognition of tricuspid stenosis. *Circulation* 22:346-64, 1960.

## 6. TRICUSPID INSUFFICIENCY

Tricuspid insufficiency affects the right ventricle just as mitral insufficiency affects the left ventricle. The symptoms and signs of organic tricuspid valve disease due to rheumatic heart disease are identical with those resulting from right ventricular failure due to any cause. The valvular lesion can be suspected in the presence of mitral disease by noting a relatively early onset of right heart failure and a harsh systolic murmur along the lower left sternal border which is separate from the mitral murmur and which often increases in intensity during and just after inspiration.

### Treatment.

Tricuspid insufficiency is generally regarded as an inoperable lesion, but an attempt has been made to treat it by surgical plication of the valve annulus under direct vision if tissue deficit is not excessive.

Friedberg, C K Diseases of the Heart, 3rd ed Saunders, 1962

Muller, O., & J Shillingford: Tricuspid incompetence. *Brit.Heart J.* 16:195-207, 1954.

. . .

### Prognosis of Rheumatic Heart Disease.

Recurrent rheumatic fever may produce fatal heart failure at any time, and bacterial endocarditis is a constant threat.

A. Mitral Stenosis In general, patients with mitral stenosis die of intractable congestive failure in the 30's or 40's after a prolonged period of disability

B. Mitral Insufficiency and Aortic Valve Lesions These patients become symptomatic later in life, but death occurs within a few years after the onset of symptoms of congestive heart failure.

C. Aortic Stenosis When angina or syncope is present, sudden death usually occurs within 3 years.

D. Tricuspid Lesions These are usually associated with mitral valve disease. The prognosis is surprisingly good, with survival for up to 10 years after the onset of edema, but patients are incapacitated by fatigue.

## BACTERIAL ENDOCARDITIS

### Essentials of Diagnosis

#### Subacute

- Patient with rheumatic or congenital heart disease
- Continuous fever weight loss joint and muscle pains fatigue
- Changing murmurs splenomegaly and petechiae
- Blood culture positive

#### Acute

- Patient with acute infection or recent history of surgery or instrumentation
- High fever sudden change or appearance of new murmurs embolic phenomena petechiae and splenomegaly

The presence of fever and a heart murmur should always suggest bacterial endocarditis as the cause of the presenting cerebrovascular accident nephritis anemia hemorrhagic disorder or refractory heart failure

### General Considerations

Subacute bacterial endocarditis (SBE) is a smoldering bacterial infection of the endocardium superimposed on pre-existing rheumatic valvular or congenital heart disease. Bacteremia following a respiratory infection dental work or cystoscopy is often the initiating event but in many instances the source of infection is not known. Nonhemolytic streptococci especially *Streptococcus viridans* and *Streptococcus faecalis* are the usual etiologic agents occasionally *Staphylococcus aureus* is responsible and less commonly other organisms.

Bacteria lodge on the surface of scarred valves (usually aortic and mitral) and multiply gradually deforming the valve. Fibrin and platelet thrombi are deposited forming irregular friable vegetations which are shed as emboli to the brain peripheral arteries or viscera. Embolic glomerulonephritis or true glomerulonephritis sometimes produces renal failure. Shedding of bacteria into the blood stream from the involved valves may produce mycotic aneurysms which however rarely rupture. Active rheumatic carditis is present in 10-20% of cases.

Acute bacterial endocarditis (ABE) is a rapidly progressive infection of normal or abnormal valves usually developing in the course of heavy bacteremia or septicemia from acute infections such as pneumococcal pneumonia postabortal hysteriosalpingitis and abscesses. It may also occur as a complication of cardiac

surgery transurethral prostatectomy or surgery on infected tissue. *Diplococcus pneumoniae*, *Staphylococcus aureus*, beta hemolytic streptococci and virulent gram negative coliform organisms are the most common pathogens.

Acute endocarditis produces large friable vegetations severe embolic episodes with metastatic abscess formation and rapid perforation tearing or destruction of the affected valves.

The more common SBE produces mild to moderate systemic symptoms cerebral renal splenic or mesenteric emboli heart failure or any combination of these. The onset usually follows bacteremia from one of the sources cited above within days or weeks.

### Clinical Findings

**A. Symptoms and Signs.** Fever is present in all cases although afebrile periods may occur. Any of all of the following may occur also: night sweats chills malaise fatigue anorexia weight loss vague muscle aching arthralgia or redness and swelling of the joints sudden visual disturbances aphasia or hemiplegia due to cerebral emboli pain in the abdomen left lower chest or in the flanks due to mesenteric splenic or renal emboli nosebleeds easy bruisability and symptoms of heart failure. In ABE the course is more fulminating.

Evidence of rheumatic or congenital heart disease is usually present. Findings include tachycardia splenomegaly petechiae (especially with white centers) of the skin mucous membranes and ocular fundi or beneath the nails as splinter hemorrhages clubbing of the fingers and toes pallor or a yellowish brown tint of the skin neurologic residuals of cerebral emboli and tender red nodules of the finger or toe pads. Heart murmurs may be absent or insignificant in infection of the tricuspid and pulmonary valve where recurrent pulmonary infarction suggesting pneumonia may be a prominent feature. The clinical picture is often atypical in older persons.

ABE is essentially a severe infection associated with chills high fever prostration and multiple serious embolic phenomena. These may be superimposed on the antecedent causative infection (e.g. pneumonia furunculosis pelvic infection) or may appear abruptly following instrumentation or surgery. Heart murmurs change rapidly and heart failure occurs early.

ABE may develop during prophylactic or inadequate therapeutic antibiotic administration. In these circumstances the onset is masked and a sudden embolic episode the

appearance of petechiae, unexplained heart failure, changing murmurs, or a rising temperature may be the first clue.

**B. Laboratory Findings** In the absence of recent or concurrent antibiotic therapy, the first 2 random blood cultures (2-4 hours apart) are positive in most patients, and blood culture is positive by the third day in 85-90%. If not, urine and bone marrow cultures are indicated.

Normochromic anemia, a markedly elevated sedimentation rate, variable leukocytosis, microscopic hematuria, proteinuria, and casts are commonly present in SBE and ABE. A high BUN may be an unexpected finding, especially in older patients.

### Complications

The complications of ABE or SBE include peripheral arterial emboli (producing hemiplegias or aphasia, infarction of the bowel, kidney, or spleen, or acute arterial insufficiency of an arm or leg); congestive heart failure, renal failure, hemorrhagic tendency, anemia, and metastatic abscess formation (especially ABE). Splenic abscess may be responsible for seeming refractoriness to therapy.

### Differential Diagnosis.

SBE must be differentiated from various seemingly primary disease states. Hemiplegia, intractable heart failure, anemia, a bleeding tendency, or uremia may be caused by SBE especially in older patients. If a patient presenting with any of these illnesses has fever and a heart murmur, blood cultures should be taken immediately.

Specific diseases that require differentiation are the lymphomas, thrombocytopenic purpura, leukemia, acute rheumatic fever, disseminated lupus erythematosus, polyarteritis nodosa, chronic meningococcemia, brucellosis, and disseminated or miliary tuberculosis.

ABE masquerades as a severe systemic response to an obvious pre-existing infection. It can be recognized only by noting rapid clinical deterioration, bacteremia, the appearance or sudden change of heart murmurs, heart failure, and major embolic accidents, especially to the CNS, simulating meningitis.

### Prevention.

A high percentage of cases of endocarditis arise after dental procedures or surgery of the oropharynx and genitourinary tracts. All patients with valvular or congenital heart disease who are to have any of these procedures should be prepared in one of the following ways:

(1) 600,000 units procaine penicillin with 600,000 units crystalline penicillin, I.M., one

hour before surgery, and then 600,000 units procaine penicillin I.M. daily for 2 days.

(2) 500,000 units penicillin G or V orally 4 times daily on the day of surgery and for 2 days after surgery, and 600,000 units crystalline penicillin I.M. one hour before surgery.

(3) In case of penicillin sensitivity, give erythromycin, 250 mg. orally q.i.d. on the day of surgery and for 2 days afterward.

### Treatment.

**A. Specific Measures:** The most important consideration in the treatment of bacterial endocarditis is a bactericidal concentration of one or more antibiotics in contact with the infecting organism, which are often localized in avascular, relatively inaccessible tissues. Penicillin, because of its high degree of bactericidal activity against the great majority of bacteria which produce bacterial endocarditis, and because of its low incidence of side reactions, is by far the most useful drug. Synergistic combinations of penicillin with other antibiotics have often proved valuable. Few cases have been cured by bacteriostatic drugs used alone. Positive blood cultures are invaluable to confirm the diagnosis and to guide treatment and should be combined with tests of sensitivity of the infecting organism to various antibiotics or combinations of antibiotics. Hence one or more blood cultures should be obtained daily for 3-5 days before instituting treatment, except in desperately ill patients or patients with acute bacterial endocarditis. To avoid further heart damage, treatment should not be further delayed.

**1 Penicillin** - This drug should be given parenterally in bacterial endocarditis. The dose depends on the sensitivity of the organism, as determined by *in vitro* sensitivity tests. About 90% of strains of *Streptococcus viridans* from cases of SBE have been found to be inhibited *in vitro* by 0.1 unit/ml. or less of penicillin. However, some are quite resistant, requiring up to 10 units or more.

A minimum serum concentration many times greater than the apparent *in vitro* sensitivity of the organism must be produced to ensure a bactericidal concentration in the vegetation. After treatment has been started its success may be predicted on the basis of the ability of the patient's serum to act bactericidally against his own infecting organisms in a dilution of at least 1:100 under standard test conditions. If blood cultures have not been positive or if sensitivity tests are not available, give 10-20 million units of penicillin daily and 2 Gm. of streptomycin I.M. There are 3 alternative methods of administration: (1) For organisms sensitive to less than 0.1 U./ml. of

penicillin give 0.5-1 million units of procaine penicillin G I M twice daily (2) For organisms sensitive to 0.1 U/ml or more of penicillin give intermittent I M injections of aqueous penicillin solution every 3-6 hours (3) Continuous parenteral administration If the total daily dose is about 5 million units/day or more of penicillin give a continuous I M (or occasionally I V) drip The antibiotic can be dissolved in 1-2 L of physiologic saline or glucose solution

Approximate Dosage Schedules

Penicillin Inhibition (Bactericidal at 72 Hrs ) (units/ml )	Total Daily Penicillin Dosage (millions of units)
< 0.1	1-2 (penicillin procaine)
0.1-0.5	3-4 (aqueous)
0.5-0.9	4-5 (aqueous)
1-5	6-20 (aqueous)
> 5	20-500 (aqueous)

When bacteremia and fever persist the dosage should be doubled and redoubled until a favorable response occurs Alternatively synergistic treatment with 2 or more antibiotics may be used When high concentrations of penicillin are required probenecid (Benemid<sup>®</sup>) 0.5 Gm every 6 hours may be used to inhibit renal excretion

2 Streptomycin sulfate Intermittent I M injection gives as good levels as those obtained by I V injections Large doses are advised Give 0.5-1 Gm dissolved in 4 ml of distilled water and 1 ml of 2% procaine I M every 6 hours Observe for toxicity

3 Combined penicillin and streptomycin Accumulated evidence suggests that penicillin (5-40 million units/day) + streptomycin (2 Gm/day) may be the optimal treatment for infections due to *Streptococcus faecalis* and also for the short (2 weeks) treatment of endocarditis due to sensitive strains of *Streptococcus viridans*

4 Chlorotetracycline hydrochloride (Aureomycin<sup>®</sup>) oxytetracycline (Terramycin<sup>®</sup>) tetracycline (Achromycin<sup>®</sup>) chloramphenicol (Chloromycetin<sup>®</sup>) and erythromycin (Erythrocin<sup>®</sup>) While these drugs may suppress the progress of subacute bacterial endocarditis their use is almost always followed by a relapse Wherever possible drugs exhibiting more pronounced bactericidal activity e.g. penicillin and streptomycin should be the first

choice in treatment The exact dosages and effectiveness of therapy have not been established Nausea and vomiting result frequently from the oral administration of chlortetracycline and may interfere with treatment In such cases the drug must be given I V in doses of 50-100 mg or more every 6 hours

Although *Streptococcus faecalis* is generally inhibited by chlortetracycline oxytetracycline and tetracycline treatment with these drugs of endocarditis due to this organism is generally ineffective

5 Other drugs Neomycin bacitracin kanamycin (Kantrex<sup>®</sup>) vancomycin (Vancocin<sup>®</sup>) and ristocetin (Spontin<sup>®</sup>) may be used alone or in combination with other drugs when the organism is insensitive to less toxic antibiotics

6 Methicillin (Staphicillin<sup>®</sup>) 10-12 Gm daily I V or I M should be used in endocarditis due to penicillinase producing staphylococci

7 Combined therapy In infections due to highly resistant organisms synergistic pairs of antibiotics (as determined by tests of bactericidal activity in the laboratory) may be used (see Chapter 20) Combined therapy should never be attempted without adequate laboratory control

8 In patients exhibiting the typical features of subacute bacterial endocarditis in whom blood cultures are repeatedly negative empirical therapy with penicillin 20 million units daily by continuous I V or I M drip plus 2 Gm of streptomycin I M daily should be given for 3 weeks

9 Duration of treatment Most patients should be treated for 3-4 weeks after sterilization of the blood stream After therapy has been discontinued the patient should be observed carefully for recurrence (repeated blood cultures)

10 Recurrences Recurrences are usually evident within 1-2 weeks after therapy Occasional cases relapse months later The diagnosis of recurrence must not be made on the basis of return of fever and embolic phenomena alone these may occur for up to 6-8 weeks after therapy has ceased Positive blood cultures are essential for the diagnosis of recurrence Before re treating the patient again determine the sensitivity of the organism and then give treatment with higher dosages for a longer period of time or use a different antibiotic About 70-75% cures are now being reported

11 Anticoagulants It is generally agreed that the use of heparin or bishydroxycoumarin (Dicumarol<sup>®</sup>) in the treatment of SBE is unnecessary and may be dangerous

**B. General Measures** General supportive measures are as for any severe infection with fever.

### C. Treatment of Complications.

1. Infarction caused by emboli breaking off from the infected area usually occurs in organs in the systemic circulation, but if the endocardial lesion is on the right side of the heart the embolus may be to the pulmonary circulation. Treatment is symptomatic.

2. Cardiac failure (uncommon) - Active myocarditis or scarring of the heart valves may precipitate congestive failure. Giving large quantities of penicillin as the sodium salt may incidentally provide significant amounts of sodium ion. Therefore, in treating a patient with SBE who has congestive failure or if failure is impending use the calcium or potassium salt of penicillin.

3. Anemia, if severe, should be treated by whole blood transfusion or, if heart failure is present, red cell mass transfusions.

4. Uremia may result from focal embolic nephritis or glomerulonephritis.

### Prognosis.

Without treatment, fewer than 1% of people with ABE or SBE survive. With treatment, up to 80% of all cases are cured bacteriologically, although congestive heart failure may later supervene (especially in aortic lesions). Patients with initially negative blood cultures whose cultures remain persistently negative have the worst immediate prognosis. If significant damage to the heart valves or kidneys does not occur, the ultimate prognosis is that of the underlying cardiac disease. However, if heart failure, uremia, or dynamic aortic insufficiency develops the outcome will be fatal despite cure of infection. Fatal cerebral emboli or rupture of a mycotic aneurysm may occur months after apparent cure. Thus, 10% die because of resistant bacterial infection or relapse, and another 20% die during or after therapy from residual irreversible organ damage. Intractable heart failure due to aortic insufficiency is the commonest cause of death after bacteriologic cure.

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## ACQUIRED HEART DISEASES

### HYPERTENSIVE CARDIOVASCULAR DISEASE

The criteria for the diagnosis of hypertension are arbitrary, because the arterial pressure rises with age and varies from one occasion of measurement to another. Most authorities consider hypertension to be present when the diastolic pressure consistently exceeds 100 mm Hg in a person more than 60 years of age, or 90 mm. Hg in a person less than 50 years of age. The vascular complications of hypertension are thought to be the consequence of the raised arterial pressure.

Hypertension which has not demonstrably affected the heart is called "hypertensive vascular disease." When left ventricular hypertrophy, heart failure, or coronary artery disease is present, "hypertensive cardiovascular disease" is the appropriate term.

Hypertension in any form is uncommon before age 20. In young people it is usually caused by chronic glomerulonephritis, renal artery occlusion, pyelonephritis, or coarctation of the aorta.

Transient elevations of BP caused by excitement, apprehension, or exertion and the purely systolic elevation of BP in elderly people caused by loss of elasticity in their major arteries do not constitute hypertensive disease.

### Etiology & Classification.

**A. Essential Hypertension** In 80% of cases of hypertensive vascular or cardiovascular disease no cause can be established. The onset of essential hypertension is usually between the ages of 35 and 55. The family history is usually suggestive of hypertension (stroke, "sudden death," heart failure). Women are affected more often than men. Elevations in pressure are transient early in the course of the disease but eventually become permanent. Even in established cases the BP fluctuates widely in response to emotional stress, especially anger, resentment, and frustration. The resting BP is always lower than single office readings, and can be determined after several hours' rest in bed. BP's taken by the patient at home are lower than those recorded in the office, clinic, or hospital. Basal readings obtained during sleep are most reliable in estimating prognosis.

**Note** All of the foregoing may be true in other forms of hypertension also. A diagnosis of essential hypertension is warranted only after repeated and thorough search for specific causes has been unsuccessful.

#### B Renal Hypertension

1 **Vascular** Narrowing of one or both renal arteries due to atherosclerosis, fibromuscular hyperplasia, or other causes has come to be recognized as perhaps the most common cause of curable hypertension.

2 **Parenchymal** Chronic glomerulonephritis and pyelonephritis have in the past accounted for the largest group of known causes of hypertension. Unilateral pyelonephritis is rare but can often be cured by surgery. Polycystic kidney disease and congenital or acquired obstructive hydronephrosis are rare causes. Acute glomerulonephritis is often associated with hypertension.

C **Endocrine** Pheochromocytoma, a tumor of the adrenal medulla or (rarely) of chromaffin tissue along a sympathetic chain, causes sustained or intermittent hypertension by releasing norepinephrine and epinephrine into the blood stream. Cushing's syndrome, primary aldosteronism, and desoxycorticosterone overproduction of patients with adrenal insufficiency regularly cause hypertension. An eosinophilic tumor of the pituitary producing acromegaly may also cause hypertension.

D **Coarctation of the Aorta** Congenital constriction of the arch of the aorta produces hypertension in the upper extremities and carotid arteries. BP in the legs is normal or low.

E **Miscellaneous** Hypertension of varying severity is present in toxemias of pregnancy, increased intracranial pressure due to tumor or hematoma, overdistention of a neurogenic bladder, and in the late stages of polyarteritis nodosa, disseminated lupus erythematosus, and scleroderma.

F **Malignant Hypertension** Any form of sustained hypertension may abruptly become more severe. The diastolic pressure rises above 130 mm Hg, causing widespread arteriolar necrosis, rapidly progressive renal failure, and papilledema. Papilledema may precede renal impairment and is the best definitive clinical sign; the height of the blood response alone may be misleading. The term "malignant" is used because mortality approaches 100% in 2 years if the disease is not treated.

#### Pathogenesis

Essential and renal hypertension are due to increased peripheral arteriolar resistance of unknown mechanism. Unless heart failure or edema is present, cardiac output and blood volume are not affected in well-established cases. Renal pressor substances may play a role in essential and renal hypertension, but this has not been demonstrated in humans.

In pheochromocytoma, hypertension is due to varying combinations of increased cardiac output and peripheral resistance caused by epinephrine and norepinephrine, respectively.

The mechanism of production of hypertension by adrenal glucocorticoids, aldosterone, and desoxycorticosterone is not known.

The hypertension of coarctation of the aorta is thought to result directly from the constriction, which causes the left ventricle to eject blood into a short chamber, although the renal mechanism may be involved.

#### Pathology

Sustained hypertension causes the initially reversible arteriolar narrowing to become permanent as a result of intimal thickening, hypertrophy of the muscular coat, and hyaline degeneration. In malignant hypertension, arteriolar necrosis (especially in the renal vessels) develops rapidly and is responsible for the acute onset of renal failure. The dominant manifestations of hypertension are secondary to left ventricular hypertrophy and failure and to the widespread arteriolar lesions. Hypertension accelerates the development of coronary and cerebral artery atherosclerosis, myocardial infarction, and cerebral hemorrhage or thrombosis are common sequelae.

#### Clinical Findings

The clinical and laboratory findings are mainly referable to the degree of vascular deterioration and involvement of the target organs: heart, brain, kidneys, eyes, and peripheral arteries.

#### A Symptoms

1 **Mild to moderate essential hypertension** is compatible with normal health and well-being for many years. Vague symptoms usually appear after the patient learns he has

high blood pressure. Suboccipital headaches characteristically occurring early in the morning and subsiding during the day are common, but any type of headache may occur (even simulating migraine). Other common complaints are lightheadedness, tinnitus,

fullness in the head, easy fatigability, loss of energy, and palpitations. These symptoms are caused by anxiety about hypertension or by associated psychologic disturbances.

2 **Patients with pheochromocytoma** which secretes predominantly norepinephrine usually

have sustained hypertension. Intermittent release of epinephrine causes attacks (lasting minutes to hours) of acute anxiety, palpitation, profuse perspiration, pallor, trembling, and nausea and vomiting. BP is markedly elevated during the attack, and angina or acute pulmonary edema may occur. In primary aldosteronism, patients have recurrent episodes of generalized muscular weakness or paralysis, paresthesias, polyuria, and nocturia.

3. Cardiac involvement often leads to paroxysmal nocturnal dyspnea or cardiac asthma with or without symptoms of chronic left ventricular failure. Angina pectoris or myocardial infarction may develop.

4. Progressive renal involvement produces no striking symptoms, nocturia or intermittent hematuria may occur.

5. Peripheral arterial disease most commonly causes intermittent claudication. When the terminal aorta is narrowed or occluded, pain in the buttocks and low back pain appear on walking and men become impotent.

6. Cerebral involvement causes (1) hemiplegia or aphasia due to thrombosis or (2) sudden hemorrhage leading to death in hours or days. In malignant hypertension (and occasionally in its absence), severe headache, confusion, coma, convulsions, blurred vision, transient neurologic signs, and nausea and vomiting may occur ("hypertensive encephalopathy"). The mechanism of their production is not known. Cerebral edema may play a role.

**B. Signs** Physical findings depend upon the cause of hypertension, its duration and severity, and the degree of effect on target organs.

1. The diagnosis of hypertension is not warranted in patients under the age of 50 unless the BP exceeds 140/90 mm. Hg on at least 3 separate occasions after the patient has rested 20 or more minutes in familiar, quiet surroundings. Casual readings (i.e., those taken in the usual fashion) may be much higher than this in the absence of hypertensive disease, since with rest the pressures return to normal, this is vascular hyperactivity, not hypertension.

2. Retinas - The Keith-Wagener (KW) classification of retinal changes in hypertension has prognostic significance and correlates well with the clinical course.

KW1 = Minimal arteriolar narrowing.

KW2 = More marked narrowing and arteriovenous nicking.

KW3 = Flame-shaped or circular hemorrhages and exudates.

KW4 = Any of the above plus papilledema. i.e., elevation of the optic disk, ob-

literation of the physiologic cup, or blurring of the disk margins. By definition, malignant hypertension is always associated with papilledema.

3. Heart and arteries - A loud aortic second sound and an early systolic ejection click may occur. Evidence of left ventricular enlargement with a left ventricular heave indicates well established disease. With onset of left ventricular failure, pulmonary basal rales, gallop rhythm, and pulsus alternans may be noted, a presystolic gallop alone does not necessarily imply failure.

4. Direct comparison should be made of both carotid, radial, femoral, popliteal, and pedal pulses, and the presence or absence of bruits over major vessels, including the abdominal aorta and iliacs, should be determined. BP should be taken in both arms and legs.

5. Cerebrum - Neurologic residuals of cerebral thrombosis or hemorrhage may be present ranging from only a positive Babinski, or Hoffman reflex to frank hemiplegia.

6. Endocrine status - The signs of Cushing's disease should be noted if present trunk obesity, hirsutism, acne, purple striae, and finely-grained skin. One kidney may be displaced by an adrenal tumor. In primary aldosteronism flaccid paralysis or muscular weakness and hypoaffective or absent tendon reflexes may be noted.

7. Coarctation of aorta - Weak or delayed femoral pulses (in comparison with radial pulses) in younger people justify a diagnosis of coarctation of the aorta. Confirmatory signs are a basal systolic murmur transmitted to the interscapular area and palpable collateral arteries along the inferior rib margins and especially around the scapular borders.

8. Renal artery stenosis - A characteristic arterial bruit may be heard with a diaphragm stethoscope in the left or right epigastrium, transmitted from the affected renal artery. The bruit can often be traced into the flank and to the costovertebral angle.

9. Renal parenchymal disease - The patient may have a "uremic" appearance and odor. Polycystic kidneys are large and readily palpable.

**C. Laboratory Findings** Routine urinalysis may disclose a low fixed specific gravity compatible with advanced renal parenchymal disease or hypokalemic nephropathy of primary aldosteronism. In both, NPN is elevated and anemia due to advanced azotemia may be present. In aldosteronism, however, the serum  $K^+$  is low and the serum  $CO_2$  elevated,

the reverse is true in uremia associated with primary renal disease

Proteinuria granular casts and occasionally microhematuria occur in nephrosclerosis differentiation from chronic nephritis on this basis alone is impossible

Demonstrable bacteriuria in a fresh clean specimen suggests chronic pyelonephritis white cell casts are rarely found Pyuria is frequently absent Quantitative culture of a clean specimen must be performed on all patients and repeated at intervals since bacteriuria in chronic pyelonephritis may be intermittent

Quantitative determination of urinary excretion of 17 hydroxycorticoids or catecholamines and vanillylmandelic acid is indicated if the clinical picture suggests Cushing's disease or pheochromocytoma respectively Urinary aldosterone need not be determined routinely except in very early or borderline instances the diagnosis usually can be established by blood chemistry

#### Tests for pheochromocytoma

(1) Provocative test for a patient with normal BP Give 0.05 mg of histamine base in 0.5 ml of normal saline in a tuberculin syringe rapidly I.V. leaving the needle in the vein (so that phenolamine can be given to lower excessive BP rise in response to histamine) A BP rise of 60/30 mm Hg or a rise greater than that following a cold pressor test occurs within 2 minutes when pheochromocytoma is present

(2) Test in presence of sustained hypertension due to pheochromocytoma The baseline BP should be determined while the patient rests for 20 minutes It should exceed 170/110 mm Hg Phenolamine (Regitine®) 5 mg rapidly I.V. best given into the tubing of an infusion during which the levels of the BP have been stabilized should produce a sustained fall of at least 35/25 mm Hg within 2.5 minutes in patients with pheochromocytoma Note Sedatives antihypertensive drugs and uremia may cause a false positive test

(3) Determine 24 hour urinary catecholamines (see back endsheet) or vanillylmandelic acid (normal 0.7-6.8 mg/24 hours)

D X-ray Findings Chest x-ray may disclose rib notching and the small aortic knob of coarctation and indicate the degree of cardiac enlargement caused by hypertension I.V. urograms yield valuable information on relative renal size renal displacement the presence of obstruction and pyelonephritis and are diagnostic of polycystic disease

E ECG Findings ECG can estimate the degree of left ventricular hypertrophy and will

show signs of coronary artery disease in conduction disturbances and significant Q waves In aldosteronism the Q-T interval is prolonged

F Special Studies Pre-sacral oxygen studies for visualization of adrenal tumors renal angiography to detect and outline renal artery stenosis and determination of differential water electrolyte and dye excretion by the kidneys

If specific causes have been excluded periodic ophthalmoscopic study and evaluation of cardiac and renal status by ECG chest x-ray PSP excretion NPN urinary specific gravity and urine protein determinations are required

#### Treatment

A Hypotensive Drugs Many patients with hypertension especially middle aged women live years in comfort without treatment Great care should therefore be exercised before subjecting these patients to the disagreeable side effects and potential dangers of a continuous program of drug therapy

Hypertension varies strikingly in severity in different patients treatment at present should be varied depending upon the severity of the hypertension and the presence of complications

The least toxic drugs should be used for mild hypertension Over a period of months or years slight to moderate lowering of the BP may prevent or decrease or possibly reverse the vascular complications of hypertension Combinations of drugs are useful but they are difficult to evaluate

In most severe cases the ganglionic or postganglionic blocking agents should be considered but in most instances of less severe disease it will be worthwhile to begin with rauwolfia or chlorothalazine (or both) and then if necessary add hydralazine (Apresoline®) before the ganglionic blocking agents are resorted to

Current insurance data have shown that even slight increases in BP decrease survival especially by causing premature atherosclerosis A clinical trial program must be done before it can be determined whether treatment of mild hypertension (diastolic pressure less than 105 mm Hg) without vascular complications will prevent atherosclerosis and increase survival It is reasonable to think that treatment will do this

Indications for potent hypotensive drugs

(1) Definite Indications Hypotensive drug therapy is definitely indicated in malignant hypertension in hypertensive cardiac failure when acute myocardial infarction has been ex-



cluded, for rapidly increasing diastolic BP with left ventricular hypertrophy and dilatation or when there is evidence of deterioration in the heart and fundi (exudates and hemorrhages), especially in young (particularly male) patients.

(2) Probable indications Hypotensive drugs are probably indicated in recurrent mild cerebral thrombosis with neurologic sequelae and high diastolic pressure in intractable coronary insufficiency with high diastolic pressure, when the diastolic BP exceeds 105-110 mm. Hg without evidence of the complications of hypertension, or for severe intractable hypertensive headaches (in the absence of obvious emotional stress).

(3) Doubtful indications Hypotensive drug therapy is probably not indicated for mild benign essential hypertension in elderly women or for early transient hypertension in young people in whom there is no objective evidence of vascular deterioration or complications.

#### Hypotensive Drugs

1. Rauwolfia drugs - Rauwolfia has a relatively slight hypotensive action but may be useful because of its mild sedative effect and its value as an adjunct when combined with ganglionic or postganglionic blocking compounds, veratrum, hydralazine (Apresoline®) or chlorothiazide. Nasal stuffiness, gastric hyperacidity, sodium retention, and severe depression may occur, in which case the drug should be withdrawn. Give either of the following (1) Reserpine, 0.1-0.25 mg t.i.d. orally at onset and maintain on 0.25 mg /day Reserpine may also be given I.M., 1-2.5 mg every 8-12 hours, for a short time in hypertensive emergencies. (2) Rauwolfia (Rau-dixin®) 100-200 mg. daily

2. Hydralazine hydrochloride (Apresoline®) - The initial dosage of this drug is 10-25 mg orally b.i.d., progressively increasing to a total dosage of 200 mg./day. The results of the oral use of this drug as a sole method of therapy are often not impressive, but some patients obtain a hypotensive effect. Because hydralazine is the only hypotensive agent which increases the renal blood flow, it may be useful as an adjunct to oral methonium compounds (ganglionic blocking agents) or to chlorothiazide.

Toxic side effects are common when large doses of hydralazine are used alone but uncommon when the drug is used in combination with chlorothiazide in doses not exceeding 200 mg /day or with rauwolfia. The most important are headache and palpitations with tachycardia. A syndrome resembling diffuse collagen disease has occurred, usually after large doses have been given for many months.

3. Thiazides - Chlorothiazide and related oral diuretic agents reduce the dose required

of blocking agents to about half and synergize with other agents such as rauwolfia. Give chlorothiazide (Diuril®), 0.5-1 Gm /day in divided doses, with due caution for electrolyte depletion, especially in patients receiving digitalis, or hydrochlorothiazide (Hydro-Diuril®, Esidrix®) 50 mg 1-2 times daily.

4. Ganglionic and postganglionic blocking agents - The most frequently used of these agents are pentolinium tartrate (Ansoiyser®), chlorisondamine chloride (Ecolid®), and mecamlamine hydrochloride (Inversine®). They can be used orally or subcutaneously. With the exception of mecamlamine, absorption following oral administration is small and irregular with resultant unpredictable falls in BP. Guanethidine (Ismelin®) acts by blocking the postganglionic adrenergic neurons tolerance rarely occurs. The drug can be given in a single daily dose. It is effective and well tolerated and it does not produce parasympathetic blockade. The initial dose is 10 mg orally increasing gradually to tolerance at weekly intervals. Postural hypotension (especially in the morning on awakening and after exercise) diarrhea muscle aching and lack of ejaculation in men are the major symptoms of toxicity.

Basic principles in the use of the ganglionic and postganglionic drugs are as follows

(1) Hospitalize the patient under close supervision except when using guanethidine (Ismelin®) in which case treatment can be started on an out-patient basis. (2) Start with a small initial dose and increase gradually, depending upon the tolerance and response of the patient. (3) The degree of reduction of BP should be only moderate in the first week or so, and no attempt should be made to reduce the pressure to normal until it has been demonstrated that the patient can tolerate systolic pressures of about 160 mm. Hg without hypotensive symptoms. (4) Postural hypotension, which is greatest at the height of the effect of the drug should be considered not only as a potential danger to the patient but also as a therapeutic weapon to prolong the hypotensive action of the drug after the peak effect has worn off. (5) Minimize the dose of ganglionic blocking agent required (and thereby minimize side effects) by prior administration of reserpine, 0.25 mg /day, or thiazide drugs (see above), or both. (6) Minimize constipation by use of laxatives or, if necessary, neostigmine by mouth. (7) Warn the patient of the effects of additional vasodilatation due to heat, including hot baths, alcohol, and immobility following exercise. The effect of these drugs should be evaluated in an ambulatory patient in the erect position. Otherwise, excessive doses will be given.

**Oral ganglionic or postganglionic blocking agents** A trial of 2-3 weeks is usually required to determine the dose necessary to lower the BP to about 160/100 mm Hg. The patient may then be seen on an outpatient basis and the dose gradually increased to that level which produces the desired fall of BP. Opinion is divided about whether the desired pressure at the time of peak action of the drug is 150/160 mm Hg systolic or whether it is that which results in mild hypotensive symptoms on standing. Constipation is to be avoided in patients receiving oral methonium compounds because it increases the absorption of the drug; laxatives should be given to ensure a daily bowel movement.

Although the determination of the proper drug dosage is difficult, it is usually considered satisfactory if standing diastolic pressures of 90-100 mm Hg or less are achieved. Since the effectiveness of the drug cannot be determined by casual BP readings in the physician's office, 3 methods have been used to determine effective dosage: (1) Home BP readings are recorded and shown to the physician at his regular visits. The physician may increase or decrease the dose and the patient is instructed to decrease the dose whenever the BP falls below 150/90 and not to take a dose if the BP is below 130/80 in the recumbent position. (2) Motionless standing for one minute before taking the drug is advocated to prevent excessive hypotension. BP will then be sufficiently high so that an additional quantity can be taken without harm. This only guards against excessive dosage; it does not indicate when the dose has been inadequate. (3) Periodic hospitalization is advisable for 1-2 days to determine basal BP readings. These readings are often 50-100 mm Hg less than readings obtained in the doctor's office and can be used to control the dosage of the methonium compounds.

The initial doses of the oral ganglionic and postganglionic blocking compounds are as follows: Hexamethonium 125 mg pentolinum tartrate (Ansolyse®), 10-20 mg, chlorisondamine chloride (Ecolid®), 10-20 mg, mecamylamine hydrochloride (Inversine®) 1-2.5 mg, guanethidine (Ismelin®) 10 mg. Parenteral ganglionic blocking agent: Pentolinum tartrate (Ansolyse®), 1-2 mg subcut or 1 M, if no untoward effect occurs, the dose can be gradually increased beginning on the second day, by increments of 0.5 mg. Caution should be exercised in older patients to avoid lowering the BP too rapidly, this is true also of those patients who have evidence of atheromas in the cerebral or coronary arteries, since acute hypotension may result in thrombosis of

these vessels. On discharge from the hospital the average patient receives 5-10 mg/day orally in divided doses. After discharge the patient should be seen at frequent intervals and the dose adjusted so as to achieve the desired effect without undue faintness or side effects. In some patients in order to prevent a postural hypotension which may produce severe symptoms during this period, it may be necessary to have the patient lie down for one hour after each injection. In many of these patients, however, tolerance gradually develops although marked hypotension may still occur on standing; the patient may be able to sit or walk immediately after an injection. Patients should be warned to avoid motionless standing for an hour or so after an injection, shaving, waiting in line for a bus, and similar activities should be particularly condemned.

**Acute hypertensive emergencies.** The most important are acute hypertensive encephalopathy and acute pulmonary edema associated with a marked rise in BP in hypertensive patients with left ventricular failure. Reserpins 1-2.5 mg 1 M every 8-12 hours is often helpful. If the BUN is less than 70 mg/100 ml, the addition of a diuretic such as chlorothiazide or hydrochlorothiazide has a potentiating effect. One of the ganglionic blocking agents or guanethidine may then be given orally and reserpine given in the usual oral doses.

**Side effects and hazards of ganglionic and postganglionic blocking agents**

(1) Acute hypotensive reactions are manifested by faintness, weakness, and nausea and vomiting. The patient should be instructed to lie down immediately and place his feet higher than his head. Unless the hypotensive effect is too severe, the symptoms pass rapidly with this postural assistance. If the symptoms persist, give a vasopressor drug such as phenylephrine hydrochloride (Neo-Synephrine®) or methoxamine (Vasoxyl®) subcut or a slow continuous IV infusion of levarterenol bitartrate (Levophed®) 4 mg/L, titrated carefully because occasional patients are unusually sensitive to some vasopressors.

(2) Acute or progressive renal failure due to decreased renal blood flow or filtration pressure may necessitate discontinuing the drug.

(3) Vascular thromboses are a hazard in older patients who suffer severe falls of BP.

(4) A low sodium diet potentiates the action of blocking compounds. If an individual receiving fixed doses of the drug is given a low-sodium diet, hypotensive symptoms may occur. It is usually desirable to place the patient on a 2 Gm sodium diet at the onset of therapy.

(5) Alcohol, hot climate, vasodilator drugs, vigorous exercise, and salt depletion potentiate the action of ganglionic and postganglionic compounds.

(6) Parasympatholytic effects (due to parasympathetic blocking) - The ganglionic blocking agents (but not guanethidine) will cause blurring of vision, constipation, and dryness of the mouth, these can be corrected in part by the use of neostigmine orally in doses of 7.5-15 mg. (1/8-1/4 gr.). Simple laxatives should be tried initially for constipation.

5. Veratrum compounds - These drugs have not received wide acceptance because of the narrow margin between their therapeutic and toxic effects; nausea, vomiting, and weakness. Purified preparations, particularly protoveratrine A and B (Veralba®), are still used, especially in hypertensive emergencies in heart failure complicating acute nephritis, the convulsions of eclampsia, or hypertensive pulmonary edema, give protoveratrine as follows (1) For acute hypertension, 1.5-1.9 mcg./Kg. I.V. (hypotensive effect lasts 1-3 hours) or 1-2 mcg./Kg. I.M. every 8 hours (2) For chronic hypertension, 0.4-1.5 mg. orally 3-4 times daily after meals (average dose). The dose must be carefully regulated, at times as little as 0.5 mg. may cause sudden vomiting.

### B. Surgical Procedures

1. Sympathectomy - Most authorities now agree that sympathectomy prolongs life only when undertaken on patients with early malignant hypertension whose renal function is good

2. Adrenalectomy - The results of this radical procedure have not been impressive, although some patients with severe hypertension have received considerable benefit.

C. Low-sodium Diet A rigid low-sodium diet (containing 350 mg. of sodium or less per day) is effective in some cases, but many patients find it difficult to stay on a low-sodium diet for the months and years required. The introduction of chlorothiazide (Diuril®) has made a rigid low-sodium diet unnecessary. 2 Gm. of sodium are usually allowed.

D. Psychotherapy The hypertensive patient often has emotional conflicts, both independent of and resulting from the hypertension itself. Attempts to treat hypertensive patients with psychoanalytic methods have not been successful, although attention to the emotional needs of the patient is an important adjunct to other methods of treatment.

### E. Other Methods of Treatment

1. Sedation - For nervousness give phenobarbital, 15-30 mg. (1/4-1/2 gr.) 3-4 times daily.

2. Drugs which have evoked little general enthusiasm despite occasional favorable results, because of the unpredictable effects on the hypertension and the high incidence of unpleasant side effects, include phenoxymethamine (Dibenzylamine®) the dihydrogenated ergot preparations, tolazoline (Priscoline®), and potassium thiocyanate and the long-acting nitrates

F. Treatment of Complications The cardiac, cerebral, and renal complications of hypertension are discussed under congestive failure, angina pectoris, myocardial infarction, cerebral hemorrhage, cerebral thrombosis and renal failure

The headache of hypertension is largely due to emotional causes. Suggestion and explanation are often helpful. Hypotensive drugs are most effective in relieving severe headache associated with the malignant or pre-malignant phase of hypertension

### Prognosis.

Although many patients with slight elevation of BP live a normal span, most patients with untreated hypertensive cardiovascular disease die of complications within 20 years of onset. Before the effective hypertensive drugs were available, 70% of patients died of heart failure or coronary artery disease, 15% of cerebral hemorrhage, and 10% of uremia. Heart failure is now an uncommon cause of death, cerebrovascular, coronary artery, and renal artery complications of the basic atherosclerotic process account for the majority of deaths

The survival of patients with malignant hypertension has been markedly improved by modern drug therapy. 50-60% are now alive 5 years after diagnosis, whereas at most about 10% were alive after 2 years before the newer drugs became available

The underlying cause of hypertension may be responsible for death, as in Cushing's disease, polyarteritis, and terminal nephritis.

Hoobler, S. W.: Hypertensive Disease: Diagnosis and Treatment. Hoeber, 1959

Sokolow, M., & D. Perloff: The prognosis of essential hypertension treated conservatively. Circulation 23:697-713, 1961.

## ARTERIOSCLEROTIC HEART DISEASE (Arteriosclerotic Coronary Artery Disease, AsCAD)

Arteriosclerotic heart disease, or obliterative atherosclerosis of the coronary arteries, is the commonest underlying cause of cardiovascular disability and death. A disorder of lipid metabolism is thought to be responsible for the localized subintimal accumulations of fatty and fibrous tissue which progressively obstruct the epicardial portions of the coronary arteries and their main branches. Genetic predisposition, local clotting and hemodynamic factors, adequacy of collateral circulation, hormones and excessive intake of saturated fats over many years are thought to be interrelated contributory causes. Arterial diastolic hypertension accelerates the development of atherosclerosis. Diabetes mellitus, hypercholesterolemia (familial and acquired), and tuberosus and tendinous xanthomatosis characteristically produce advanced atherosclerosis at an early age.

Men are more often affected than women by an over-all ratio of 4:1, before the age of 40 the ratio is 8:1, and beyond age 70 it is 1:1. In men the peak incidence of clinical manifestations is age 50-60, in women, age 60-70. Advanced stages of atherosclerotic coronary artery disease, even complete occlusion, may remain clinically silent, being discovered incidentally after death due to other causes. At present, the only means of determining the location and extent of narrowing is coronary angiography, which is still an experimental procedure. There is no correlation between the clinical symptoms and signs and the extent of disease.

The pathophysiology underlying the clinical manifestations of arteriosclerotic heart disease may be listed as follows:

Clinical Expression	Mechanism
1. Angina pectoris	1. Transient, localized myocardial ischemia
2. Acute myocardial infarction	2. Complete arterial occlusion
3. Intermediate between (1) and (2)	3. Prolonged myocardial ischemia with or without myocardial necrosis
4. Heart failure, chronic arrhythmias, conduction disturbances, abnormal ECG	4. Gradual fibrosis of myocardium or conduction system. May result from (2) or (3) also.
5. Sudden death.	5. Any of the above

## 1. ANGINA PECTORIS

### Essentials of Diagnosis

- Squeezing or pressure-like pain, retrosternal or slightly to the left, which appears quickly during exertion, may radiate in a set pattern, and subsides with rest.
- Seventy per cent have diagnostic ECG abnormalities after mild exercise, the remaining 30% have normal tracings or nondiagnostic abnormalities.

Angina pectoris is most often confused with chest pain of musculoskeletal or dorsal root origin, neurocirculatory asthenia, upper gastrointestinal tract disease or disease of the left shoulder. Differentiation is based upon analysis of the pain and the specific measures which precipitate or relieve the pain.

### General Considerations.

Angina pectoris is usually due to arteriosclerotic heart disease, but in rare instances it may occur in the absence of significant disease of the coronary arteries as a result of severe aortic stenosis or insufficiency, syphilitic aortitis, increased metabolic demands as in hyperthyroidism or after thyroid therapy, marked anemia, or paroxysmal tachycardias with very rapid ventricular rate. The underlying mechanism is a discrepancy between the myocardial demands for oxygen and the amount delivered through the coronary arteries. The 3 groups of variables which determine the production of relative or absolute myocardial ischemia are as follows:

(1) Limitation of oxygen delivered by the coronary arteries (a) Vessel factors include atherosclerotic narrowing, collateral circulation, and reflex narrowing in response to emotion, cold, upper gastrointestinal disease, or smoking. (b) Blood factors consist of anemia, hypoxemia, and polycythemia (increased viscosity). (c) Circulatory factors are fall in BP due to arrhythmias, orthostatic hypotension, bleeding, and Valsalva's maneuver, and decreased filling pressure of the coronary arteries due to aortic stenosis or insufficiency.

(2) Increased cardiac output. Physiologic factors are exertion, excitement, digestion and metabolism following a heavy meal. Pathologic factors (high-output states) include anemia, thyrotoxicosis, arteriovenous fistula and pheochromocytoma.

(3) Increased myocardial demands for oxygen. May be due to increased work of the heart, as in aortic stenosis, aortic insuf-

ciency, and diastolic hypertension, or increased oxygen consumption due to thyrotoxicosis or in any state characterized by increased catecholamine excretion (pheochromocytoma, strong emotion, and hypoglycemia).

#### Clinical Findings.

A. History. The diagnosis of angina pectoris depends almost entirely upon the history, and it is of the utmost importance that the patient be allowed to describe the symptoms in his own way, using his hands to demonstrate the location and quality of the symptom. The history should specifically include the following categories

1. *Circumstances that precipitate and relieve angina* - Angina most commonly occurs during walking, especially up an incline or a flight of stairs. Exertion which involves straining, closing the glottis, and immobilizing the thorax precipitates an attack most rapidly. Regardless of the type of activity, angina occurs during exertion and subsides promptly if the patient stands or sits quietly. Patients prefer to remain upright rather than lie down. Some patients obtain relief by belching, and for this reason may attribute their distress to "stomach trouble." The amount of activity required to produce angina varies with each patient, but it is always less after meals, during excitement, or on exposure to a cold wind. Heavy meals and strong emotion can provoke an attack in the absence of exertion.

2. *Characteristics of the discomfort* - Patients often do not refer to angina as a "pain" but as a sensation of squeezing, burning, pressing, choking, aching, bursting, "gas," or tightness. It is commonly attributed to "indigestion." The distress of angina is never a sharply localized or darting pain which can be pointed to with a finger. It appears quickly during exertion, and increases rapidly in intensity until the patient is compelled to stop and rest even though the discomfort may not be severe.

3. *Location and radiation* - The distribution of the distress may vary widely in different patients but is always the same for each individual patient. In 80-90% of cases the discomfort is felt behind or slightly to the left of the sternum. When it begins farther to the left or, uncommonly, on the right, it characteristically moves centrally and is felt deep in the chest. Although angina may radiate to any segment from C2 to T10, it radiates most often to the left shoulder and upper arm, frequently moving down the inner volar aspect of the arm to the elbow, forearm, wrist, or fourth and fifth fingers. Radiation to the right

shoulder and distally is less common, but the characteristics are the same. Occasionally angina may be referred to, or felt initially in, the lower jaw, the base or back of the neck, the interscapular area, or high in the left back.

Angina may almost certainly be excluded when the patient designates the *only* site of pain by pointing to the area of the apical impulse with one finger.

4. *Duration of attacks* - Angina is of clearly defined short duration, and subsides completely without residual discomfort. If the attack is precipitated by exertion and the patient promptly stops to rest, the distress of angina usually lasts less than 3 minutes (although most patients think it is longer). Attacks following a heavy meal or which are brought on by anger often last 15-20 minutes.

5. *Effect of glyceryl trinitrate* - The diagnosis of angina pectoris is strongly supported (1) if 0.4 mg. ( $\frac{1}{150}$  gr.) of glyceryl trinitrate (nitroglycerin) invariably shortens an attack and (2) if that amount taken immediately beforehand invariably permits greater exertion before the onset of angina or prevents angina entirely. However, this source of diagnostic information is less reliable than the characteristic history.

6. *Unrelated disorders that intensify angina* should be considered. Cholecystitis, sliding hiatus hernia, thyrotoxicosis, paroxysmal arrhythmias, orthostatic hypotension, or left ventricular failure may account for unusual variants of angina pectoris.

B. Signs. Examination during a spontaneous or induced attack frequently reveals a significant elevation in systolic and diastolic BP, occasionally gallop rhythm is present during pain only. Carotid sinus massage often causes the pain to subside more quickly than usual if it slows the cardiac rate, and is a helpful maneuver in instances of "atypical angina."

It is important to detect signs of diseases that may contribute to arteriosclerotic heart disease, e.g., diabetes mellitus (retinopathy or neuropathy), xanthomatosis (tuberosa, plana, or tendinosa), or disorders that intensify the angina, such as hypertension, thyrotoxicosis, orthostatic hypotension, and aortic stenosis or mitral stenosis.

The cardiovascular examination is normal in 25-40% of patients with angina. In the remainder, evidence of occlusive disease of the peripheral arteries, hypertensive retinopathy and cardiomegaly, significant murmurs, or signs of cardiac failure may be noted.

C. Laboratory Findings. Anemia, hypercholesterolemia, diabetes mellitus, hypo-

glycemia hyperthyroidism and upper gastrointestinal diseases should be investigated as possible contributory factors STS should be done routinely

**D ECG Findings** The resting ECG is normal in 25% of patients with angina In the remainder abnormalities include atrioventricular or intraventricular conduction defects patterns of left ventricular hypertrophy old myocardial infarction or nonspecific ST T changes

An exercise test may be warranted if the diagnosis is seriously in doubt Do not do an exercise test unless the resting ECG is normal the patient has had no digitalis for 3 weeks and the onset of the pain is not of recent origin These precautions are necessary to prevent exercising a patient with acute or subacute myocardial ischemia A positive ECG exercise test consists of at least a 2 mm horizontal depression or definite sag of the entire ST segment in one or more leads Depression of the ST junction alone ( J ) flattening of T waves or minor ST segment depression is not diagnostic In the standardized test significant changes occur in only 50-60% of patients with angina The percentage is much higher when tracings are taken during a spontaneous attack or if a more extensive exercise test is used

#### Differential Diagnosis

A Psychophysiologic cardiovascular reactions are a loosely defined group of disorders having in common dull aching chest pains often described as heart pain lasting hours or days often aggravated by exertion but not promptly relieved by rest Darting knife-like pains of momentary duration at the apex or over the precordium are often present also Emotional tension and fatigue make the pain worse Dyspnea of the hyperventilation variety palpitation fatigue and headache are also usually present Continual exhaustion is a frequent complaint

The anterior chest wall syndrome is characterized by sharply localized tenderness of intercostal muscles pressure on which reproduces the chest pain Sprain or inflammation of the chondrocostal junctions which may be warm swollen and red (so called Tietze's syndrome) may result in diffuse chest pain which is also reproduced by local pressure

Xiphoid tenderness and lower sternal pain may arise from and be reproduced by pressure on the xiphoid process

Any of the above may occur in a patient with angina

**B Cervical or thoracic spine disease** (degenerative disk disease postural strain arthritis) involving the dorsal roots produces sudden sharp severe chest pain similar to angina in location and radiation but related to specific movements of the neck or spine recumbency and straining or lifting Pain due to cervical thoracic disk disease involves the outer or dorsal aspect of the arm and the thumb and index fingers rather than the ring and little fingers

**C Peptic ulcer chronic cholecystitis cardiospasm and functional gastrointestinal disease** are often suspected because some patients indisputably obtain relief from angina by belching In these disorders symptoms are related to food intake rather than exertion X-ray and fluoroscopic study are helpful in diagnosis The pain is relieved by appropriate diet and drug therapy

**D Hiatus hernia** is characterized by lower chest and upper abdominal pain after heavy meals occurring in recumbency or upon bending over The pain is relieved by bland diet antacids semi Fowler position and walking

**E Degenerative and inflammatory lesions of the left shoulder cervical rib and the scalenus anticus syndrome** are differentiated from angina by the fact that the pain is precipitated by movement of the arm and shoulder paresthesias are present in the left arm and postural exercises and pillow support to the shoulders in bad give relief

**F Tight mitral stenosis or pulmonary hypertension** resulting from chronic pulmonary disease can on occasion produce chest pain which is indistinguishable from angina pectoris including ST segment sagging or depression The clinical findings of mitral stenosis or of the lung disease are evident and the ECG invariably discloses right axis deviation or frank right ventricular hypertrophy

#### Treatment

##### A Treatment of the Acute Attack

1 Glyceryl trinitrate (nitroglycerin) is the drug of choice it acts in about 1-2 minutes As soon as the attack begins place one 0.3 mg ( $\frac{1}{100}$  gr) tablet under the tongue and allow it to dissolve The dose may be increased to 0.4-0.6 mg ( $\frac{1}{150}$   $\frac{1}{100}$  gr) if no relief is obtained from a smaller dose Glyceryl trinitrate may be used freely whenever an attack occurs or may be used in order to prevent an attack (see below) It may cause headache and hypotension

2. Amyl nitrite, one pearl crushed and inhaled, acts in about 10 seconds. This drug usually causes flushing of the face, pounding of the pulse, and sometimes dizziness and headache. These reactions may be minimized by inhaling the drug from a distance or by rapidly passing the crushed pearl before the nose. The patient soon learns how to vary the amount of drug he wishes to inhale.

3. Longer-acting nitrates and other drugs have no place in the therapy of the acute attack.

4. Alcohol - 30-60 ml. (1-2 oz.) of whisky or brandy may be a helpful home remedy.

5. General measures - The patient should stand still or sit or lie down as soon as the pain begins and remain quiet until the attack is over. This is the natural reaction of most patients, but some try to "work the attack off" and patients should be warned against this.

#### B. Prevention of Further Attacks

1. Long-acting nitrates - Pentaerythritol tetranitrate (Peritrate<sup>®</sup>), 10 mg. orally t.i.d. before meals, and erithrityl tetranitrate (Cardilate<sup>®</sup>), 10-15 mg. sublingually t.i.d. The success of the long-acting preparations has not been proved.

2. Glyceryl trinitrate (nitroglycerin), 0.3-2.0 mg. (1/200-1/100 gr.) under the tongue just before activity.

3. Xanthines may be of some benefit orally in large doses (see p. 236).

4. Other techniques - Obese patients with protuberant abdomens who have angina may have fewer attacks if proper abdominal support is given. The mechanism is not clear. The Kerr-Lagen belt is designed for this purpose. Surgical procedures have been employed only in patients with severe incapacitating angina pectoris in whom medical treatment has failed, the results to date have been unimpressive. The objective of production of myxedema by means of thiouracil compounds or radio-active iodine (see Chapter 17) is to reduce the work of the heart. Good results have been reported in about half of cases of intractable angina, but this method should not be used until prolonged rest and attention to the emotional needs of the patient have ruled out a transient reversible coronary insufficiency.

5. General measures - The patient must avoid all habits and activities that he knows will bring on an attack. Coexisting disorders (especially anemia) which may lead to increased cardiac ischemia must be treated. Most patients with angina do not require prolonged bed rest, but rest and relaxation are beneficial. Adequate mental rest is also im-

portant. Obese patients should be placed on a reducing diet low in animal fats and their weight brought to normal or slightly subnormal levels. Tobacco is best avoided or used in moderation because it produces tachycardia and elevation in BP.

Hypercholesterolemia has been shown to be associated with premature atherosclerosis in man and to be essential in its production in animals. It has not been shown that lowering the serum cholesterol level will reverse the atherosclerotic process. However, if the serum cholesterol exceeds 250 mg./100 ml. in a patient with angina pectoris, an attempt should be made to lower it by diet, with total calories containing about 25% fat (60% vegetable and 40% animal). If this is unsuccessful, beta-sitosterol (Cytellin<sup>®</sup>) may be added, one or 2 Tbsp immediately before each meal. Nicotinic acid in large doses has been used to lower serum cholesterol, but its toxicity has not been established.

#### Prognosis.

The course is prolonged, with variable frequency and severity of attacks punctuated by periods of complete remission and episodes of myocardial infarction, or terminated by sudden death. The average survival after onset of angina is 8-10 years, and the annual mortality attributable to angina is 5-8% above that expected on the basis of age and sex. Diabetes mellitus, hypertension, cardiomegaly, congestive failure, myocardial infarction, arrhythmias, and conduction defects (as shown on ECG) shorten the life expectancy. Onset prior to age 40 or a family history of early cardiac death is prognostically unfavorable.

Half of all patients die suddenly, and an additional third after myocardial infarction. Heart failure accounts for a portion of the remainder of deaths.

De la Chapelle, C. E.: The recognition of angina pectoris. *Circulation* 21:1061-4, 1960.

Logue, B.: Treatment of intractable angina pectoris. *Circulation* 22:1151-5, 1960.

## 2. VARIANTS OF ANGINA PECTORIS

#### Angina Decubitus.

Patients with otherwise typical angina may on occasion have an attack shortly after going to bed or may be awakened by an attack. Sitting or standing up brings relief slowly, and glyceryl trinitrate is not as effective as usual.

Such episodes are usually brief and infrequent. If this variant appears suddenly occurs nightly, and especially if pain recurs during the night, conditions that intensify angina must be sought. If none are found, this type of angina decubitus is indicative of impending myocardial infarction, and the death rate is high if patients are not treated accordingly.

#### Intractable Angina (Status Anginosus, Coronary Failure, Coronary Insufficiency).

Aggravating factors such as thyrotoxicosis and undue emotional tension must be diligently sought, for they account for 5-10% of cases. A high percentage of patients with prolonged anginal-type pain develop frank myocardial infarction or die suddenly. Some patients suddenly revert to their usual pattern of angina or become asymptomatic. Only rarely does a patient continue to have prolonged chest pain, presumably from myocardial ischemia without evidence of myocardial necrosis.

If adequate doses of glyceryl trinitrate are not effective, treat as for myocardial infarction. If pain persists after myocardial infarction has been ruled out, therapeutic myxedema with thiouracil compounds or radioactive iodine should be considered.

#### Anginal Pain as a Precursor to Myocardial Infarction.

Patients should be treated as for myocardial infarction in the following situations (1) Sudden onset of angina pectoris with long duration of individual attacks (2) Rapid build-up in frequency, severity, and duration (3) Abrupt change in location or radiation (4) Association of nausea or vomiting with pain. (5) Persistent or repetitive angina decubitus (6) Complete refractoriness to glyceryl trinitrate.

Reappearance of angina after a long asymptomatic interval may or may not require treatment as for myocardial infarction.

## ACUTE MYOCARDIAL INFARCTION

### Essentials of Diagnosis

- Sudden but not instantaneous development of crushing anterior chest pain producing hypotension or shock.
- Rarely painless, masquerading as acute congestive heart failure, syncope, cerebral thrombosis, or "unexplained" shock.
- Fever, leukocytosis, rising sedimentation rate, elevated SGOT and LDH within 24-48 hours.
- ECG Abnormal Q waves, elevated ST, later, symmetric inversion of T waves.

In 90% of cases the diagnosis of acute myocardial infarction is clear-cut, based on the typical pain, appearance of hypotension or shock, and subsequent ECG and laboratory evidence of myocardial necrosis. Dissecting aneurysm, acute pericarditis, pulmonary embolism, ailing hiatus hernia, cervical arthritis, or severe cardiac neurosis may cause diagnostic confusion initially.

### General Considerations.

Myocardial infarction is ischemic necrosis of a localized area of the myocardium due to sudden occlusion of a coronary artery by thrombus formation or subintimal hemorrhage at the site of atheromatous narrowing. Less often, complete occlusion by proliferation of the intimal plaques or by hemorrhage into a plaque is responsible. Infarction may occur in the absence of complete occlusion if coronary blood flow is temporarily reduced, as in postoperative or traumatic shock or gastrointestinal bleeding or hypotension due to any cause. Rarely, embolic occlusion, syphilitic aortitis, or acute vasculitis cause infarction.

The location and extent of infarction depend upon the anatomic distribution of the vessel, the site of current and previous occlusions, and the adequacy of collateral circulation. Thrombosis occurs most commonly in the anterior descending branch of the left coronary artery, resulting in infarction of the anterior left ventricle. Occlusion of the left circumflex artery produces anterolateral infarction. Right coronary thrombosis leads to infarction of the posteroinferior portion of the left ventricle.

### Clinical Findings.

#### A Symptoms

1. Premonitory pain - In over one-third of patients, alteration in the pattern of an-



gina, sudden onset of atypical angina, or unusual "indigestion" felt in the chest precedes myocardial infarction by hours, days, or several weeks.

2. Pain of infarction - This may begin during rest (even in sleep) or activity. It is similar to angina in location and radiation but is more severe, does not subside with rest, and builds up rapidly or in waves to maximum intensity in the space of a few minutes or longer. Glyceryl trinitrate has no effect. The pain lasts for hours if unrelieved by narcotics, and is often unbearable. The patient breaks out in a cold sweat, feels weak and apprehensive, and moves about, seeking a position of comfort. He prefers not to lie quietly. Light-headedness, syncope, dyspnea, orthopnea, cough, wheezing, nausea and vomiting, or abdominal bloating may also be present, singly or in any combination.

3. Painless infarction - In about 5% of cases, pain is absent or minor and is overshadowed by the immediate complications notably acute pulmonary edema or rapidly developing heart failure, profound weakness, shock, syncope, or cerebral thrombosis.

**B Signs** Physical findings are highly variable, and the apparent clinical severity of the episode does not necessarily correlate well with the extent or location of the infarction.

1. Shock may be described as a systolic BP below 80 mm Hg (or slightly higher with prior hypertension) along with gray facial color, mental dullness, cold clammy skin, peripheral cyanosis, tachycardia or bradycardia, and weak pulse. Shock is present only in severe attacks. Shock may be caused primarily by the pain rather than the hemodynamic effects of the infarction, if so, distinct improvement occurs within 30-60 minutes after relief of pain and administration of oxygen.

2. Cardiac effects - In the severe attack, the first and second heart sounds are faint, often indistinguishable on auscultation, and assume the so-called "tic-tac" quality. Gallop rhythm, distended neck veins, and basal rales are often present. Acute pulmonary edema or rapidly progressive congestive failure may dominate the picture. In less severe attacks, examination is normal or there may be diminished intensity of the first sound or low systolic BP. Pericardial friction rub appears in 20-30% of cases between the second and fifth days. It is often transient or intermittent.

3. Fever is absent at the onset (in contrast to acute pericarditis) and during prolonged shock. It usually rises to 37.8-39.4°C (100-103°F.) - rarely to 40.6°C. (105°F.) - within

24 hours and persists for 3-7 days - rarely longer.

**C Laboratory Findings** Leukocytosis of 10-20 thousand cells/cu.mm usually develops on the second day and disappears in one week. The sedimentation rate is normal at onset, rises on the second or third day, and remains elevated for 1-3 weeks. SGOT activity increases in 6-12 hours, reaches a peak in 24-48 hours, and returns to normal in 3-5 days. Serum lactic acid dehydrogenase may remain elevated for 5-7 days. Serial determinations are helpful in equivocal instances.

**D ECG Findings** ECG changes do not correlate well with the clinical severity of the infarction. The characteristic pattern consists of specific changes which undergo a stereotyped "evolution" over a matter of weeks in the average case. At the onset there is elevation of ST segment and T wave and abnormal Q waves. The ST segment progressively returns to the baseline as T waves become symmetrically inverted. An unequivocal ECG diagnosis of infarction can only be made in the presence of all 3 abnormalities. Serial ST-T changes alone are compatible with but not diagnostic of infarction. The characteristic changes are not seen in the presence of left bundle branch block or when a previous infarct has permanently altered the ECG. Even in these instances however an ECG taken early in an attack often shows ST segment displacement.

#### Differential Diagnosis

In acute pericarditis, fever often precedes the onset of pain, which is predominantly pleuritic and is significantly relieved by breathing and specific body positions. The friction rub appears early, is louder, is heard over a greater area, and is more persistent than in infarction, and a pleuropericardial rub is often also present. There are no QRS changes, and T wave inversion is more widespread without reciprocal changes (except in aVR). SGOT and LDH are rarely elevated.

Dissecting aneurysm causes violent chest pain which is often of maximum severity at onset. It typically spreads up or down the chest and back over a period of hours. Changes in pulses, changing aortic murmurs, and left pleural effusion or cardiac tamponade are distinctive features. BP does not fall early. Syncope or neurologic abnormalities are common. ECG changes are not diagnostic of infarction unless the coronary ostia are involved in the proximal dissection.

Acute pulmonary embolism may cause chest pain indistinguishable from myocardial

infarction as well as hypotension, dyspnea, and distended neck veins, but the ECG, regardless of coronary-like changes, will usually show right axis deviation. SGOT and LDH are often elevated, as in myocardial infarction. If the attack is not fatal, pulmonary infarction follows, frequently causing pleuritic pain, hemoptysis, and localized lung findings. Thrombophlebitis will usually be found on careful examination of the legs, groins, and lower abdomen.

Cervical or thoracic spine disease produces sudden, severe chest pain similar to myocardial infarction, but orthopedic measures give relief and the ECG is normal.

Hiatus hernia may simulate the pain of infarction, and the T waves may be flat or even inverted during the attack, but there is no hypotension or subsequent fever, leukocytosis, or increase in sedimentation rate. SGOT, or LDH.

Acute pancreatitis and acute cholecystitis may superficially mimic infarction. A past history of gastrointestinal symptoms, present findings in the abdomen, jaundice, elevated serum amylase, and x-ray findings differentiate these. Most helpful is the absence of diagnostic serial ECG changes.

Spontaneous pneumothorax, mediastinal emphysema, the pre-eruptive phase of herpes zoster, and severe psychophysiological cardiovascular reactions may also have to be differentiated from myocardial infarction.

### Complications

Congestive heart failure may be present at onset or may develop insidiously or abruptly following an arrhythmia or pulmonary embolization. Sedation and weakness may mask the presence of dyspnea and orthopnea, distention of neck veins, persistent basal rales, gallop rhythm, an enlarging tender liver, and sacral edema should be sought daily.

If anticoagulants are not given, pulmonary embolism secondary to phlebitis of the leg or pelvic veins occurs in 10-20% of patients during the acute and convalescent stage.

Arrhythmias occur in 20% or more of patients. Ventricular premature beats are most common, atrial fibrillation and prolonged atrioventricular conduction are next most common. Complete heart block, atrial tachycardia or flutter, and ventricular tachycardia are rare. A Stokes-Adams attack is an infrequent complication.

Cerebrovascular accident (due to thrombosis) may result from a fall in BP associated with myocardial infarction. It is advisable to take an ECG in all patients with "cerebrovascular accident."

Recurrent myocardial infarction or extension of the infarction occurs in about 5% of patients during recovery from the initial attack.

Rupture of the heart is uncommon. When it occurs it is usually in the first week.

Perforation of the interventricular septum is very rare, characterized by the sudden appearance of a loud, harsh systolic murmur and thrill over the lower left parasternal area and acute heart failure.

Ventricular aneurysm and peripheral arterial embolism may occur early or not for months after recovery.

The shoulder-hand syndrome is a preventable disorder caused by prolonged immobilization of the arms and shoulders, possibly due to "reflex sympathetic dystrophy." Early pain and tenderness over the affected shoulder is followed by pain and swelling and weakness of the hand with excessive or deficient sweating.

Oliguria, anuria, or, rarely, tubular necrosis may result if shock persists.

### Treatment.

#### A. Immediate Treatment

1. Rest - Attempt to allay apprehension and anxiety. Physical and mental rest in the most comfortable position is essential during the first 2-3 weeks, when rupture of the heart is most apt to occur. The patient should not be allowed to feed or care for himself during the first few days unless the attack is mild without shock or other complications. Special nursing care is highly desirable. A bedside toilet probably requires less effort than the use of a bedpan.

Adequate sleep is as vital in patients with myocardial infarction as it is with those suffering from cardiac failure. Sedatives should be used as necessary to provide sufficient sleep, and morphine derivatives should not be withheld in the first few days if they are indicated.

2. Analgesia - Give morphine sulfate 10-15 mg. ( $\frac{1}{16}$ - $\frac{1}{4}$  gr.) slowly I.V. If the pain is not relieved in 15 minutes, repeat this dosage. Further injections can be given subcut. 6-15 mg. ( $\frac{1}{8}$ - $\frac{1}{4}$  gr.) as necessary for continued relief. The subcutaneous route is used unless the attack is severe or the patient is in shock. If the patient is in shock with severe pain, slow I.V. administration may be necessary. Caution: Do not give a second dose of morphine if respirations are below 12/minute.

Meperidine and dihydromorphinone are preferred by some clinicians because they are said to produce less nausea and vomiting. The dosage of dihydromorphinone (Dilaudid<sup>®</sup>) is

4 mg. ( $\frac{1}{16}$  gr.) I.M. or I.V. The dosage of meperidine (Demerol®) is 50-100 mg. I.V. or I.M. as needed.

Aminophylline, 0.5 Gm. ( $\frac{7}{12}$  gr.) I.V. very slowly (1-2 ml. per minute), may be helpful if the pain is not relieved by opiates or oxygen (see below).

3. Oxygen is often useful and sometimes necessary for the relief of dyspnea, cyanosis, pulmonary edema, shock, and chest pain.

4. Shock is a frequent and serious complication, with an estimated mortality of 80% particularly when it is delayed until after the pain has subsided. Present evidence suggests that vasopressor drugs (sympathetic amines) may elevate the BP and decrease mortality in myocardial infarction associated with shock. Shock must be treated early to achieve the best results. For details of the use of vasopressor drugs, see p. 4. A hypotonic myocardium often accompanies acute myocardial infarction, and shock may be associated with an increased venous pressure. Some clinicians therefore favor digitalization as for congestive failure (see p. 233) in the shock of acute myocardial infarction. The increased cardiac output increases coronary flow, and the pressure may rise.

Shock may be the result of undetected ventricular tachycardia or other arrhythmias, and prompt treatment of this complication (see below) may be life-saving. Venous and arterial transfusions have not been very effective but should be kept in mind as adjuncts.

5. Anticoagulant therapy is a controversial matter in the milder cases (rapid relief of pain, minimal signs of myocardial necrosis, absence of shock or cardiac failure). In severe cases of myocardial infarction, anticoagulants are generally recommended.

Cerebrovascular accident occurring as a complication of myocardial infarction requires treatment for both diseases. For treatment of cerebrovascular accident, see Chapter 15. For technic of administration, see p. 155.

**B. Follow-up** Alert clinical observation for evidence of extension of the infarction, new infarction, the appearance of complications, or symptoms requiring treatment is essential. Recurrent pain days or weeks after the initial pain has subsided suggests extension of the myocardial necrosis, confirmation should be sought in the ECG and in other clinical features. The same methods of treatment are used as for the first infarction, but a further period of rest is required.

### C. Treatment of Complications

1. If cardiac failure develops, treat as for failure due to any cause. Oxygen, low-

sodium intake, diuretics, and cautious digitalization are the essential features of treatment. Potassium salts should be employed (potassium chloride, 1 Gm. t.i.d.) if diuretics are given to a patient receiving digitalis and a low-sodium diet. The patient should be digitalized in such a manner as to avoid toxic reactions if possible. Rapid digitalization is best avoided unless the need is urgent. If the cardiac failure is mild and manifested solely by pulmonary rales and increased dyspnea, restriction of sodium and the administration of mercurial or thiazide diuretics may be sufficient. Digitalis is avoided by some authorities because of the hazard of ventricular arrhythmias, but its well-controlled administration should not be deferred if cardiac failure demands it.

2. Arrhythmias - Ventricular premature beats are common. They indicate increased irritability of the damaged myocardium and may presage ventricular tachycardia. Quinidine sulfate is the drug of choice (see p. 234). An alternative to quinidine is procainamide (see p. 238) or, if digitalis is thought to be responsible for the arrhythmia, potassium salts.

Ventricular tachycardia is an emergency (see p. 213).

Atrial fibrillation is usually transient. If this persists, if the patient tolerates it poorly, or if congestive heart failure occurs, digitalize with care (see p. 231).

3. Stokes-Adams attack with heart block is an emergency (see p. 215).

4. Thrombo-embolic phenomena are common during the course of myocardial infarction. Anticoagulants should be administered promptly (see p. 155). For treatment of pulmonary embolism, see p. 155.

5. Oliguria, anuria, acute tubular necrosis - see Chapter 26.

6. Shoulder-hand syndrome - Best treated by preventive physical therapy instituted early.

7. Rupture, perforation of the interventricular septum, and aneurysm - No treatment is available.

8. Activity status in convalescence - The minimum period of rest should be at least 3 weeks, if the infarction has been very severe, this should be increased to about 6 weeks. The program for most patients is one month of complete rest, one month of slowly increasing activity, and a third month of restricted activity before returning to work. The amount of rest should be individualized according to the severity of the myocardial infarction and the response of the patient.

The patient should not be permitted to walk freely about the room for about 7-10 days after

he is first allowed out of bed. Gradual resumption of activity is most important. He should remain on the same floor with gradually increasing periods of walking slowly and without producing chest pain, dyspnea, undue tachycardia or fatigue. When first allowed out of doors usually not until 2 months after the infarction, he should avoid hills and stairs for another month.

### Prognosis

The over all mortality during the first month after the infarction averages 30%. In the mild attack clinical manifestations subside promptly and the initial mortality is less than 5%. Clinically severe myocardial infarction may require 6-12 weeks for full recovery. The mortality rises to 60-90% with prolonged shock, severe early heart failure, leukocytosis over 25,000 with eosinophilia, fever above 40°C (104°F), uncontrolled diabetes mellitus, old age and previous definite infarction, especially if these occur in combination. Pulmonary embolism which is not treated with anticoagulants, persistent arrhythmias, and extension of the infarct superimpose a mortality of 15-20% during early convalescence.

Long term survival is related to the availability of medical care and the presence of other chronic diseases in addition to the

residuals of infarction. Complete clinical and ECG recovery is compatible with survival of 10-15 years. Patients with residual heart failure, arrhythmia or angina die within 3-6 years.

Gertler M M, & others. Clinical aspects of coronary heart disease. J A M A 145: 1291-5, 1951.

Sampson J J. Coronary Heart Disease. Clinical Cardiopulmonary Physiology. Grune & Stratton, 1960.

## DISTURBANCES OF RATE & RHYTHM

The presence of a significant arrhythmia should be suspected in any of the following circumstances: (1) When there is a history of sudden onset and sudden termination of palpitation or rapid heart action. (2) when the heart rhythm is grossly irregular. (3) when the heart rate is below 40 or above 140/minute. (4) when the heart rate does not change with breath holding or exercise. (5) when a rapid heart rate suddenly slows during carotid sinus

### TREATMENT OF CARDIAC ARREST OR VENTRICULAR FIBRILLATION

#### External Cardiac Massage

External cardiac massage consists of rhythmic application of manual pressure to the lower third of the sternum. It must be started within 3-5 minutes after arrest and combined with simultaneous mouth-to-mouth ventilation of the lungs. The patient is placed supine on a firm surface, with the physician standing or kneeling above him. The heel of one hand is placed on the lower sternum with the heel of the other hand on top of it and firm pressure is applied vertically once every second, so that the sternum moves about 3-5 cm (depending upon size and body build) toward the vertebral column. The pressure is completely released after each maneuver. Pressure on the ribs and liver should be avoided.

Mouth-to-mouth ventilation should be maintained by an assistant if the physician is alone. He should interrupt massage every 30 seconds to ventilate the lungs with 3 or 4 deep breaths.

Palpable pulses and constriction of the pupils are signs of adequate circulation.

An ECG should be obtained as soon as possible.

#### Ventricular Defibrillation

If ventricular fibrillation is present a 0.25-sec 440 volt shock will usually defibrillate the heart. More than one shock may be necessary in some cases. Vasopressors (e.g. epinephrine) and drugs to reverse acidosis (molar sodium lactate) may be valuable.

massage, (6) when the first heart sound varies in intensity, or (7) when a patient develops sudden anginal pain, shock, congestive heart failure, or syncope. The complete diagnosis of an arrhythmia consists of accurate identification of the abnormality and proper assessment of its significance. The most common arrhythmias are sinus arrhythmia, sinus tachycardia, sinus bradycardia, atrial and ventricular premature beats, and paroxysmal atrial tachycardia. These occur in normal and diseased hearts alike and have no significance except insofar as they alter circulatory dynamics. Atrial fibrillation and flutter occur most commonly in patients with arteriosclerotic or rheumatic heart disease, but thyrotoxicosis, acute infections, or trauma may precipitate them in the absence of heart disease. Ventricular tachycardia is the most serious disorder of rhythm and appears most often in the presence of advanced coronary artery disease. Partial or complete heart block also results most commonly from coronary artery disease. From the physiologic standpoint, arrhythmias are harmful to the extent that they reduce cardiac output, BP, and coronary or cerebral arterial blood flow. Rapid heart rates may cause any or all of these changes and, in the presence of heart disease, may precipitate acute heart failure or pulmonary edema, angina pectoris or myocardial infarction, and syncope or cerebral thrombosis. Patients with otherwise normal hearts may tolerate rapid rates with no symptoms other than palpitation or fluttering, but prolonged attacks usually cause weakness, exertional dyspnea, and precordial aching. Unusually slow heart rates rarely produce symptoms at rest or even during moderate exertion unless the ventricular rate falls below 30, at which point weakness and exertional dyspnea begin to appear. If the heart rate abruptly slows, as with the onset of complete heart block or transient standstill, syncope or convulsions may result.

Arrhythmia of physiologic or abnormal variety should be diagnosed when (1) the heart rate is slower than 60 or faster than 100/minute, (2) the rhythm is irregular regardless of rate, (3) an abnormal pacemaker is dominant, or (4) a disturbance of atrioventricular conduction is present.

If possible, elicit a history of previous attacks and precipitating factors, symptoms of heart failure, and anginal pain. Examine for cardiac enlargement, significant murmurs, signs of heart failure, and hypotension. Count the heart rate for one minute. If the rate is seemingly regular, repeat the count twice to determine if the rate is absolutely regular, if

irregular, determine whether pulse deficit is present. If there is no severe failure, angina, or recent infarction, determine the effects of breath-holding, exercise, and change of position on the heart rate and rhythm. Massage the right and left carotid sinus successively for 30 seconds while listening to the heart, cease massage as soon as a change in rate occurs. Note whether the first heart sound varies in intensity. Examine the neck veins for abnormal pulsations.

The final diagnosis of arrhythmias depends upon the ECG. However, consideration of the patient's age, the type of associated heart disease, and the results of the examination permit a diagnosis in most cases before the ECG is taken.

Friedberg, C. K. Cardiac arrhythmias. *Progr. Cardiovas. Dis.* 2:319-33, 1960.  
Lown, B., Wyatt, N. F., & H. D. Levine: Paroxysmal tachycardia with block. *Circulation* 21:129-43, 1960

## SINUS ARRHYTHMIA

Sinus arrhythmia is a cyclical increase in normal heart rate with inspiration and decrease with expiration. It results from reflex changes in vagal influence on the normal pacemaker and disappears with breath-holding or increase of heart rate due to any cause. It has no significance except in older persons, when it may be associated with coronary artery disease.

See References above.

## SINUS TACHYCARDIA

Sinus tachycardia is a heart rate faster than 100 beats/minute due to rapid impulse formation by the normal pacemaker secondary to fever, exercise, emotion, anemia, shock, thyrotoxicosis, or drug effect. The rate may reach 180 in young persons but rarely exceeds 160. The rhythm is basically regular, but serial one-minute counts of the heart rate indicate that it varies 5 or more beats/minute with changes in position, breath-holding, sedation, or correction of the underlying disorder.

The rate slows gradually, but tachycardia may begin abruptly in response to sudden emotional stimuli.

See references on p 209

### SINUS BRADYCARDIA

Sinus bradycardia is a heart rate slower than 60 beats/minute due to increased vagal influence on the normal pacemaker. It increases after exercise or administration of atropine. It has no significance except when the rate is below 40; elderly patients may then develop weakness or even syncope.

See references on p. 209.

### ATRIAL PREMATURE BEATS

Atrial premature beats occur when an ectopic focus in the atria fires off before the next expected impulse from the sinus node. Ventricular systole occurs prematurely and the compensatory pause following this is only slightly longer than the normal interval between beats. Such premature beats occur with equal frequency in normal or diseased hearts and are never sufficient basis for a diagnosis of heart disease. Speeding of the heart rate by any means abolishes premature beats.

See references on p 209

### PAROXYSMAL ATRIAL TACHYCARDIA

This is the commonest paroxysmal tachycardia. It occurs more often in young patients with normal hearts. Attacks begin and end abruptly, and usually last several hours. The heart rate may be 140-240/minute and is perfectly regular, i.e., the rate will not vary more than 1-2 beats/minute. Exercise, change of position, and breath-holding have no effect. Carotid sinus massage or induced gagging or vomiting either have no effect or promptly abolish the attack. Patients are asymptomatic except for awareness of rapid heart action. In prolonged attacks with rapid rates, dyspnea or tightness in the chest may be felt. Paroxysmal atrial tachycardia may result

from digitalis toxicity, and then is associated with A-V block so that only every second or, rarely, every third atrial impulse reaches the ventricles (so-called PAT with block).

#### Prevention of Attacks.

A. Attempt to find and remove the cause especially emotional stress, fatigue, or excessive use of alcohol or tobacco.

#### B Drugs

1 Quinidine sulfate, 0.2-0.6 Gm, (3-9 gr) 3-4 times daily, may be used to prevent frequent and troublesome attacks. Begin with small doses and increase if the attacks are not prevented and toxic effects do not occur.

2 If quinidine is not effective or not tolerated, full digitalization and maintenance may prevent or decrease the frequency of attacks.

3 Procainamide hydrochloride (Prorestyl<sup>®</sup>) in a maintenance dosage of 250-500 mg. t.i.d. may be tried if quinidine and digitalis are not successful.

#### Treatment of the Acute Attack.

In the absence of heart disease, serious effects are rare. Most attacks subside spontaneously and the physician should not use remedies that are more dangerous than the disease. Particular effort should be made to terminate the attack quickly if it persists for several days. If cardiac failure, syncope, or anginal pain develops, or if there is underlying cardiac disease.

A Mechanical Measures A variety of methods have been used to interrupt attacks and the patient may learn to do these himself. These include Valsalva's maneuver (holding the breath and contracting the chest and abdominal muscles), stretching the arms and body, lowering the head between the knees, and breath-holding.

#### B Vagal Stimulation

1 Carotid sinus pressure - With the patient relaxed in the semi-recumbent position, firm but gentle pressure and massage are applied first over one carotid sinus for 10-20 seconds and then over the other. Pressure should not be exerted on both carotid sinuses at the same time. Continuous auscultation of the heart is required so that carotid sinus pressure can be withdrawn as soon as the attack ceases. Carotid sinus pressure will interrupt about half of the attacks, especially if the patient has been digitalized or sedated.

2. Bilateral eyeball pressure has been recommended, but it is rarely as effective as

carotid sinus pressure and involves the risk of detaching the retina.

3. Induced vomiting (except in cases of syncope, anginal pain, or severe cardiac disease).

C. Drug Therapy: If mechanical measures fail and the attack continues (particularly if the above symptoms are present), drugs should be employed. There is no unanimity of opinion about the most effective drugs, but the following are satisfactory: (1) Digitalis orally or, if no digitalis has been given in the preceding 2 weeks, i.v. (2) Neostigmine (Prostigmin®), 1 mg. ( $\frac{1}{160}$  gr.) subcut (3) Procainamide hydrochloride (Pronestyl®) (see p. 238). Continuous ECG's or continuous monitoring of the heart rate and BP is essential (4) Pressor agents. (5) Quinidine sulfate (see p. 234). (6) Syrup of ipecac, 4-8 ml. (1-2 dr.) may be used to induce vomiting. It may be repeated if unsuccessful. (7) Methacholine chloride (Mecholyt®), 10 mg ( $\frac{1}{6}$  gr.) subcut. is often effective but produces unpleasant side effects and should rarely be used.

D. Cessation of Drug Therapy Paroxysmal atrial tachycardia, usually with 2:1 block, may be due to digitalis toxicity (increased dosage or excessive potassium diuresis). Treatment consists of stopping digitalis and diuretics and treating the patient for digitalis toxicity with potassium.

See references on p. 209.

## ATRIAL FIBRILLATION

Atrial fibrillation is the commonest chronic arrhythmia. It occurs most frequently in rheumatic heart disease, especially mitral stenosis, and arteriosclerotic heart disease. It may appear paroxysmally before becoming the established rhythm in thyrotoxicosis. Infection, trauma, surgery, poisoning, or excessive alcohol intake may cause attacks of atrial fibrillation in patients with normal hearts. It is the only common arrhythmia in which the ventricular rate is rapid and the rhythm irregular. An ectopic atrial pacemaker fires 400-600 times/minute. The impulses pass through the atria at varying speeds and are mostly blocked at the A-V node. The ventricular response is completely irregular, ranging from 80 to 160 beats/minute in the untreated state. Because of the varying stroke volumes induced by the varying periods

of diastolic filling, not all ventricular beats result in a palpable peripheral pulse. The difference between the apical rate and pulse rate is the "pulse deficit", this deficit is greater when the ventricular rate is high. Exercise intensifies the irregularity when the heart rate is slow. Carotid sinus massage has no effect or causes only slight slowing.

### Prevention

See Paroxysmal Atrial Tachycardia, p. 210.

### Treatment.

#### A. Paroxysmal Atrial Fibrillation

1. Digitalis is the drug of choice, especially when the arrhythmia occurs in persons with organic heart disease (particularly mitral stenosis) or with rapid ventricular rates, or when the symptoms or signs of cardiac failure have appeared. In case of doubt about whether to use quinidine or digitalis first, digitalis should be given because it controls the ventricular rate by producing an A-V block, which is the immediate objective of treatment. The objective of treatment with quinidine is to abolish the atrial ectopic rhythm, and it is quite safe to wait until the ventricular rate is brought under control with digitalis. Give full digitalizing doses with the objective of slowing the ventricular rate to 70-80/minute and avoiding toxic manifestations. In paroxysmal fibrillation there is no clear evidence that the use of digitalis will result in established fibrillation.

2. In those cases where an attack of atrial fibrillation persists in an otherwise normal heart with a ventricular rate under 140 and with no other symptoms or signs of cardiac failure, quinidine sulfate may be used at once to convert the rhythm to sinus rhythm. If the ventricular rate becomes very rapid or if symptoms of dyspnea, anginal pain or severe palpitations are produced conversion with quinidine should be temporarily suspended and digitalis given.

B. Chronic Atrial Fibrillation Opinion varies, but the following indications for conversion of atrial fibrillation serve as a general guide. Each case must be individualized. In general, conversion is attempted whenever it is thought that the patient will be better off with sinus rhythm than with atrial fibrillation. (1) Atrial fibrillation persisting after thyrotoxicosis has been treated surgically or by other means. (2) Atrial fibrillation of a few weeks' duration in an individual with no or only slight cardiac disease. (3) Atrial fibrillation associated with frequent embolic phe-

nomena. (4) Refractory cardiac failure induced by the atrial fibrillation. (5) Severe palpitations due to inability to decrease the ventricular rate with digitalis this may be obvious only on exertion. (6) Atrial fibrillation appearing for the first time postoperatively in patients with a technically successful mitral valvulotomy.

1. Digitalis - Thorough digitalization is the first step (see p 231) The patient is then usually placed on maintenance digitalis indefinitely. The object of digitalization is to slow the ventricular rate and to improve myocardial efficiency.

2. Quinidine is used to abolish the ectopic rhythm once the ventricular rate is controlled with digitalis. It is potentially hazardous and should be used only in carefully selected cases by a physician thoroughly familiar with the drug and by a method which ensures close medical supervision (preferably in the hospital) while conversion to sinus rhythm is being attempted. Caution See p. 235 for dangers of quinidine therapy.

See references on p 209

## ATRIAL FLUTTER

Atrial flutter is uncommon and usually occurs in patients with rheumatic or coronary heart disease or as a result of quinidine effect on atrial fibrillation. Ectopic impulse formation occurs at rates of 250-350, with transmission of every second third or fourth impulse through the A-V node to the ventricles. The ventricular rate is usually one-half the atrial rate (2:1 block) or 150/minute. Carotid sinus massage causes sudden slowing or standstill, with rapid return of the rate to the original level on release of pressure. When the ventricular rate is 75 (4:1 block), exercise may cause sudden doubling of the rate to 150 (2:1 block). The first heart sound varies slightly in intensity from beat to beat.

### Prevention

Similar to prevention of atrial tachycardia.

### Treatment.

A. Paroxysmal Atrial Flutter Treatment is similar to that of paroxysmal atrial tachycardia except that digitalis and quinidine are the drugs of choice. The arrhythmia tends to become established more often than does atrial or nodal tachycardia.

## B Chronic Atrial Flutter

1. Digitalis is the drug of choice. It increases the A-V block and prevents a 2:1 or 1:1 conduction. In about half of cases atrial fibrillation or sinus rhythm results from full digitalization. If atrial fibrillation due to digitalis remains, quinidine may be added to convert to sinus rhythm. Digitalis may be given by any of the usual methods. Oral medication is usually sufficient, although the I.V. route may be used if the situation is critical. Digitalis must often be given in larger doses than are usually required for cardiac failure. When a fixed 4:1 conduction is produced by digitalis, a slightly increased dose may convert the flutter to atrial fibrillation or sinus rhythm.

2. Quinidine should not as a rule be used to treat atrial flutter unless the patient is fully digitalized with a slow ventricular rate, because of the danger of producing a 1:1 conduction. If digitalis results in only a 4:1 conduction or produces atrial fibrillation which does not spontaneously convert to sinus rhythm quinidine may be given.

See references on p 209

## NODAL RHYTHM

The A-V node may assume pacemaker activity for the heart, usually at a rate of 40-60 beats/minute. This may occur in normal hearts, myocarditis, coronary artery disease or as a result of digitalis therapy. The rate responds normally to exercise and the diagnosis is often a surprise finding on ECG. Careful examination of the jugular pulse may reveal the presence of cannon waves. Patients are asymptomatic.

See references on p 209

## NODAL TACHYCARDIA

This uncommon arrhythmia is due to rapid, perfectly regular impulse formation in the A-V node with regular transmission to the ventricles. The usual rates are 140-240/minute. Nodal tachycardia may be a benign condition or may reflect serious myocardial disease, it is more common than other arrhythmias in cor pulmonale.

Treatment is along the same lines as for atrial tachycardia.

See references on p. 209.



## VENTRICULAR PREMATURE BEATS

Ventricular premature beats are similar to atrial premature beats in mechanism and manifestations but are much more common. Together, they are the commonest causes of a grossly irregular rhythm with a normal heart rate. Ectopic impulse formation causes ventricular contraction to occur sooner than the next expected beat. The sound of this contraction is audible and is followed by a longer than normal pause since the next expected beat does not occur (compensatory pause). The interval between the preceding normal beat and the beat following the compensatory pause is exactly twice the normal interval between beats in the case of ventricular premature beats, and slightly less than this with atrial premature beats. Single premature beats which occur after every normal beat produce bigeminy. Exercise generally abolishes premature beats, and the rhythm becomes regular.

Premature beats have no definite significance unless they arise from multiple foci, occur with rapid ventricular rates or in runs, or appear when digitalis is given. Severe myocardial disease or digitalis toxicity may then be responsible, but in the vast majority of instances premature beats have no significance.

### Treatment.

If no associated cardiac disease is present and if the ectopic beats are infrequent and produce no palpitations, no specific therapy is indicated.

If ventricular premature beats are due to digitalis toxicity, withdraw digitalis and diuretics for 3-5 days or until the arrhythmia disappears and then resume medication in smaller dosage. At times, however, patients with cardiac failure who are receiving digitalis may develop ventricular premature beats which are due not to digitalis toxicity but to inadequate digitalization and cardiac failure. If in doubt as to the cause, withdraw digitalis for several days and treat the cardiac failure with other available methods (see p. 218). In these circumstances, the ventricular premature beats often disappear as the cardiac failure improves.

Potassium salts, 1-3 Gm. (15-45 gr.) q.i.d., are often helpful in ventricular premature beats of digitalis origin.

Quinidine should be used orally to abolish ventricular premature beats when they occur following acute myocardial infarction or when they occur in runs or from several foci in patients with heart disease.

See references on p. 209.

## PAROXYSMAL VENTRICULAR TACHYCARDIA

This is an uncommon serious arrhythmia due to rapid ectopic impulse formation in the ventricles. The rate may be 160-240. It usually lasts hours but may persist for days. The rhythm is almost completely regular, but less so than in atrial tachycardia, and the first sound may vary slightly in intensity from beat to beat. Carotid sinus massage has no effect.

Paroxysmal ventricular tachycardia usually occurs after myocardial infarction or as a result of digitalis toxicity. Pain due to myocardial ischemia, fall in BP, and shock are common.

### Prevention

The drugs of choice are quinidine and procainamide.

### Treatment.

#### A Average Case

1 Quinidine, 0.4 Gm. (6 gr.) orally every 2 hours for 3 doses if the attack is well tolerated and the patient is not in shock. If the attack continues and there is no toxicity from the quinidine, increase the dose to 0.6 Gm. (9 gr.) every 2 hours for 3 doses. This usually terminates the attack. If it does not, give the drug I V. or I M. or change to procainamide.

2 Procainamide hydrochloride (Pro-nestyl®), 0.5-1.5 Gm. orally every 4-6 hours, may be substituted for quinidine if quinidine is ineffective or produces toxic symptoms.

#### B More Severe Case (or when other medication has failed)

1 Quinidine gluconate, 0.8 Gm. (12 gr.) or 0.5 Gm. (7½ gr.) of quinidine base, may be given I M. and repeated every 2 hours for 2-3 doses.

2 Procainamide hydrochloride (Pro-nestyl®), 0.5-1 Gm. may be given I M. and repeated in 4 hours.

#### C. Urgent Case

1. Procainamide hydrochloride (Pro-nestyl®), 1 Gm. slowly I V. (at a rate not to exceed 100 mg./minute). During the infusion, continuous ECG or, at least, repeated BP determinations are essential. Severe hypotension may result from this medication.

2. Quinidine may be given I V. as quinidine gluconate, 0.8 Gm. (12 gr.) diluted with 50 ml. of 5% glucose slowly (1 ml./minute) with continuous ECG and determination of BP. When giving I V. quinidine in severe cases

(particularly when the previous rhythm was complete A V block) the physician should be alert to the possibility of precipitating ventricular fibrillation or asystole (see cardiac arrest p 208)

3 Vasopressor drugs for shock If shock is present as a result of ventricular tachycardia or results from the drugs given 1 V it can be treated with vasopressor drugs as described under the treatment of shock (see p 4)

4 Other drugs (1) Magnesium sulfate 10 ml of a 20% solution 1 V Calcium salts should be readily available to counteract magnesium toxicity (2) 1 V morphine or meperidine (Demerol<sup>®</sup>) is sometimes successful

5 Digitalis is usually contraindicated in ventricular tachycardia however in some patients with cardiac failure in whom the above mentioned drugs have failed to restore sinus rhythm full digitalization given carefully has been successful

See references on p 209

## VENTRICULAR FLUTTER & FIBRILLATION

These arrhythmias represent more advanced stages of ventricular tachycardia in which the rate of impulse formation is more rapid and transmission becomes irregular resulting in ineffective ventricular contractions. Diagnosis can be established only by ECG. Ventricular flutter fibrillation is rapidly fatal unless terminated by drugs or defibrillation. It is usually associated with severe myocardial damage but may be precipitated by epinephrine quinidine or digitalis.

### Treatment

#### A Medical Treatment

1 Prophylactic quinidine sulfate Treatment is rarely effective unless flutter fibrillation occurs in short paroxysmal attacks in these circumstances prophylactic quinidine administration may be tried

2 Procainamide hydrochloride (Pronestyl<sup>®</sup>) may be injected into the ventricle to produce cardiac arrest. The heart may then be stimulated by epinephrine or external massage

#### B Surgical and Mechanical Measures

External cardiac massage and electric defibrillation is the treatment of choice and may be life saving (For details see p 208). Surgical exposure of the heart with direct car-

diac massage is infrequently performed today except during cardiac operations

See references on p 209

## DISTURBANCES OF CONDUCTION

### SINO ATRIAL (S A) BLOCK

In S A block the normal pacemaker fails to initiate the depolarizing impulse at its regular or regular intervals or rarely in a fixed 2:1 ratio. This failure is apparently due to heightened vagal tone and is not related to the presence of heart disease. Exercise and atropine therefore abolish S A block. This arrhythmia can be recognized by the fact that no sound is audible during the prolonged interval between beats (in contrast to ventricular premature beats). There are no symptoms unless the period of standstill extends over the span of several beats in which case momentary faintness or even syncope may occur. In susceptible individuals carotid sinus massage induces S A block.

### Treatment

In most cases no treatment is required. The causative factors should be eliminated if possible. The following drugs may be tried: (1) Atropine sulfate 0.6 mg (1/100 gr) q 1 d orally. (2) Ephedrine sulfate 25 mg (3/8 gr) orally q 1 d.

Rowe J C & P D White Complete heart block clinical followup study. *Ann Int Med* 49:250-70 1958

Wolff L Syndrome of short P R interval with abnormal QRS complexes and paroxysmal tachycardia. *Circulation* 10:282-91 1954

### ATRIOVENTRICULAR (A V) BLOCK

A V block consists of prolongation of the conduction time of the normal impulse from the atria to the ventricles. It is classified, according to the degree of block as (1) prolonged conduction (latent heart block) (2) incomplete or partial heart block and (3) complete heart block.

**Prolonged Conduction (Latent Heart Block):**

The P-R interval is prolonged to 0.22 seconds or more, but every atrial impulse reaches the ventricles. Its presence can be suspected clinically when the first heart sound is faint in the presence of a vigorous apical impulse. There may be a presystolic gallop rhythm due to audible atrial contraction. A-V block is most commonly seen in acute rheumatic fever and coronary artery disease, and as a result of treatment with digitalis or quinidine.

**Incomplete or Partial Heart Block:** In incomplete heart block the delay in conduction increases to the point where an impulse does not reach the ventricles, resulting in failure of ventricular contraction, i.e., every so often a beat is dropped. When a beat is skipped, the bundle recovers for a while; the cycle may therefore be repeated regularly or irregularly, in the former producing a 2:1 or 3:1, etc., rhythm. The diagnosis is made by noting that the intervals between heart beats in which no sound is audible is twice as long as normal (see Ventricular Premature Beats). Incomplete heart block occurs most often in arteriosclerotic heart disease. Diphtheria is a rare cause.

**Complete Heart Block:** This usually occurs only in older patients with arteriosclerotic heart disease. Occasionally it is congenital. Transmission of atrial impulses through the A-V node is completely blocked, and a ventricular pacemaker maintains a slow, regular ventricular rate, usually less than 45 beats/minute. Exercise does not increase the rate. The first heart sound varies greatly in loudness, wide pulse pressure, changing systolic BP level, and cannon venous pulsations in the neck are also present. Patients are asymptomatic unless the ventricular rate is continually below 30, weakness and heart failure then occur. During periods of transition from partial to complete heart block, certain patients have ventricular asystole which lasts several seconds to minutes. Syncope occurs abruptly, and if the asystole is prolonged beyond a few seconds convulsive movements appear (Stokes-Adams syndrome). Asystole of 2-3 minutes is usually fatal.

**Treatment.**

**A. Prolonged Conduction and incomplete Heart Block:** In the absence of Stokes-Adams syndrome (see below), treatment of A-V conduction defects is rarely successful except by elimination of drugs, if they are causative, or by the subsidence of acute myocarditis. Prolongation of the A-V conduction itself needs no treatment unless there is complete heart block with ventricular rates below 35/min. Cardiac

failure or weakness may occur with slow ventricular rates. Ephedrine or isoproterenol (Aludrine<sup>®</sup>, Isuprel<sup>®</sup>) should be given to increase the rate of the ventricular pacemaker.

**B. Complete Heart Block and Stokes-Adams Syndrome** Try to eliminate or treat the cause. The objective of treatment is to obtain an idioventricular pacemaker discharging at a rate of 35/minute or more

1. Ephedrine sulfate, 25-60 mg. (3/8-1 gr.) orally q. i d., is often effective. The dose must be sufficient to prevent the attacks. If necessary, secobarbital sodium (Seconal<sup>®</sup>), 30 mg. (1/2 gr.), may be given with each dose of ephedrine.

2. Isoproterenol hydrochloride (Aludrine<sup>®</sup>, Isuprel<sup>®</sup>) 5-15 mg., may be given sublingually 3 or 4 times daily or oftener.

3. Epinephrine - If attacks are frequent and are not controlled with ephedrine or isoproterenol, epinephrine, 0.5 ml. (8 min.) of 1:1000 solution, may be given every 8 hours as needed, or 0.2 ml. (3 min.) of a 1:1000 solution may be given subcut. every 2 hours.

4. Intracardiac epinephrine injection, 0.5 ml. (8 min.) of a 1:1000 solution, may be given if cardiac standstill persists.

5. Steroids occasionally reverse complete A-V block if it is of recent onset. Steroid therapy should be tried before internal pacemakers are used

6. Molar sodium lactate has been recommended but is not often successful.

7. Implantation of myocardial electrodes with platinum wires tunneled to a zinc-cadmium battery placed subcutaneously in the abdomen, with remote control of the rate of discharge of the battery, is now technically feasible and may be life-saving.

See references on p. 214.

**BUNDLE-BRANCH BLOCK (BBB)**

BBB is purely an ECG diagnosis based on widening of the QRS interval to 0.12 second or more. It is caused by delayed conduction through the right or left branch of the bundle of His or the myocardium. Heart rate and rhythm are not affected. Arteriosclerotic heart disease is the usual cause, but congenital lesions may be responsible.

There is no specific treatment for bundle-branch block. Treat the underlying disease.

See references on p. 214.

## ACCELERATED-CONDUCTION SYNDROME (Wolff-Parkinson-White)

The Wolff-Parkinson-White syndrome is a rare condition in which there is a rapid atrial to ventricular conduction producing a characteristic ECG with a P-R interval of less than 0.1 second and slurring of the upstroke of the QRS, resulting in an apparently abnormally prolonged QRS interval. Patients are subject to attacks of paroxysmal supraventricular tachycardia but generally do not have underlying heart disease.

See references on p. 214.

## CONGESTIVE HEART FAILURE

### Essentials of Diagnosis

- Left ventricular failure. Exertional dyspnea and fatigue, orthopnea, paroxysmal nocturnal dyspnea.
- Right ventricular failure. Elevated venous pressure, hepatomegaly, dependent edema.
- Both. Cardiomegaly, gallop rhythm, prolonged arm-to-tongue circulation time.

The individual symptoms and signs found in heart failure may occur in a wide variety of conditions. It is essential for diagnosis that there be unequivocal cardiomegaly along with the symptoms of left-sided or right-sided failure (or both). Chronic constrictive pericarditis or chronic pericardial effusion can exactly simulate chronic congestive heart failure in the absence of myocardial or valvular disease.

### General Considerations.

Congestive heart failure is a clinical syndrome which develops eventually in 50-60% of all patients with organic cardiovascular disease. It is defined as the clinical state resulting from inability of the heart to expel sufficient blood for the metabolic demands of the body. Heart failure may therefore be present when cardiac output is high, normal, or low, regardless of the absolute level, it is reduced relative to metabolic demands.

The left or right ventricle alone may fail initially, but combined failure is the rule in most cases. Failure of the right ventricle

secondary to pulmonary parenchymal or vascular disease is termed "cor pulmonale" or "pulmonary heart disease" and is discussed in Chapter 7.

The most common underlying causes of cardiac insufficiency are hypertension, coronary atherosclerosis, and rheumatic heart disease. Less common causes are chronic pulmonary disease, congenital heart disease, syphilitic aortic insufficiency, calcific aortic stenosis, and bacterial endocarditis. Numerous rare causes of heart failure include collagen diseases, arteriovenous fistula, myocarditis, beriberi, and myocardial involvement by tumors or granulomas.

In 50% of cases there are demonstrable precipitating diseases or factors. The commonest of these are arrhythmias, respiratory infection, myocardial infarction, pulmonary embolism, rheumatic carditis, excessive or rapid administration of parenteral fluids, pregnancy, thyrotoxicosis, anemia, and excessive salt intake.

### Etiology.

The basic causes of ventricular failure are as follows:

A. Myocardial Weakness or Inflammation  
Coronary artery disease, myocarditis

B. Excess Work Load

1. Increased resistance to ejection - Hypertension, stenosis of aortic or pulmonary valves.

2. Increased stroke volume - Mitral insufficiency, tricuspid insufficiency, aortic insufficiency, congenital left-to-right shunts.

3. Increased body demands - Thyrotoxicosis, anemia, pregnancy, A-V fistula.

### Pathogenesis.

The ventricle responds to each of the mechanisms listed above initially by hypertrophy. When increased strength of contraction is no longer sufficient, the diastolic filling pressure and volume increase, maintaining normal cardiac output for a time. Eventually, however, the cardiac output is insufficient to meet the metabolic demands of the body tissues. At this point cardiac insufficiency exists.

### Clinical Findings.

A. Symptoms and Signs

1. Left ventricular failure - Left ventricular failure is characterized predominantly by symptoms: dyspnea, exertional fatigue and weakness, and nocturia. Exertional dyspnea which is caused by pulmonary vascular engorgement, resembles the normal ventilatory

response to exercise but is associated with increased awareness of breathlessness and difficulty in breathing. In heart failure, the patient regularly becomes short of breath during an amount of exertion which previously caused no difficulty. As the pulmonary engorgement progresses, less and less activity brings on dyspnea until it is present even when the patient is at rest (rest dyspnea). Orthopnea, or shortness of breath occurring in recumbency which is promptly relieved by propping up the head or trunk, is precipitated by the further increase in pulmonary engorgement on recumbency. Paroxysmal nocturnal dyspnea may appear at any time and is often the first indication of left ventricular failure caused by severe hypertension, aortic stenosis or insufficiency, or myocardial infarction. It also occurs in patients with tight mitral stenosis in advanced stages. It is an exaggerated form of orthopnea, the patient awakening from sleep gasping for breath, and compelled to sit or stand up for relief. Cough is frequently present. For unknown reasons, patients may have inspiratory and expiratory wheezing (so-called cardiac asthma). The paroxysmal cough and dyspnea may pass in a few minutes to several hours, or may progress to acute pulmonary edema. Patients become pale or frankly cyanotic, sweat profusely, and complain of great air hunger. Cough productive of frothy white or pink sputum is characteristic. The attack may subside in one to several hours, on the left ventricle may progressively weaken, leading to shock and death.

These forms of dyspnea must be distinguished from those occurring commonly in many other conditions. Advanced age, debility, poor physical conditioning, obesity, chronic pulmonary disease, or severe anemia commonly produce exertional dyspnea. Extreme obesity, ascites from any cause, abdominal distention from gastrointestinal disease, or advanced stages of pregnancy may produce orthopnea in the absence of heart disease. Bronchial asthma appearing in middle life may be symptomatically indistinguishable from the paroxysmal nocturnal dyspnea of left ventricular failure. Patients with neurocirculatory asthenia or anxiety states with psychophysiological cardiovascular reactions may suffer from many kinds of dyspnea.

Accurate determination of the arm-to-tongue circulation times and systemic venous pressure is helpful in differential diagnosis of dyspnea if its cardiac origin is in question.

Exertional fatigue and weakness are early symptoms and disappear promptly on resting. Severe fatigue, rather than dyspnea, is the chief complaint of patients with mitral stenosis who have developed pulmonary hypertension.

Nocturia occurs as a result of the excretion of edema fluid accumulated during the day; it reflects the decreased work of the heart at rest and often the effects of diuretics administered during the day.

In the absence of overt right ventricular failure, examination should disclose the following: (1) The basic cause of the left ventricular failure (hypertension, aortic or mitral valve disease); (2) left ventricular hypertrophy, in which the apical impulse is forceful or heaving, displaced to the left and downward, confirmed by ECG and chest x-ray, and (3) a prolonged arm-to-tongue circulation time. The following may or may not be present, and are not necessary for diagnosis: Basilar parenchymal rales which do not clear on coughing, gallop rhythm, pulsus alternans, and an accentuated pulmonary component of the second sound ("P2"). The chest x-ray may reveal left atrial enlargement in the case of mitral stenosis, and pulmonary vascular congestion, and shows unquestioned left ventricular enlargement in the usual case.

2. Right ventricular failure - Right ventricular failure is characterized predominantly by signs. It develops after left ventricular failure of even short duration. Mitral stenosis, pulmonary valve stenosis, and tricuspid insufficiency, and such complications of congenital disease as Eisenmenger's syndrome resulting from interventricular or interatrial septal defect may produce relatively pure right ventricular failure. Tricuspid stenosis produces the same effects as right ventricular failure. Anorexia, bloating, or exertional right upper abdominal pains are common, reflecting hepatic and visceral engorgement secondary to elevated venous pressure. Oliguria is present in the daytime, polyuria at night. Headache, weakness, or mental aberration are present in severe cases.

The venous pressure can be estimated by noting the extent of jugular filling (during normal expiration) above the level of the clavicles when the patient is propped up so that his trunk makes a 30° angle with the bed. Right ventricular hypertrophy in pure right failure is easily demonstrated by lower sternal or left parasternal systolic lift or forceful pulsations independent of the apical impulse. The liver is enlarged. Ascites is rarely prominent, when it appears early and in massive amounts, cardiac tamponade, constrictive pericarditis, or tricuspid stenosis should be considered. Dependent edema caused by heart failure usually is first noted in (or is more prominent in) the left leg. The edema subsides overnight initially, but eventually persists and increases in extent. Pleural effusion is more common on the right side. Coolness of the extremities and cyanosis of the nail beds are due to

peripheral blood flow. Sinus tachycardia is present

The ECG findings indicate pure right ventricular hypertrophy in pure right-sided failure, mixed hypertrophy in Eisenmenger's syndrome, and, usually, evidence of left ventricular hypertrophy or coronary artery disease when left-sided failure is the basic cause

Chest x-ray discloses cardiac enlargement and, in advanced stages, pleural effusion. Right atrial and ventricular enlargement are readily seen in pure right heart failure but are not evident when this is secondary to left ventricular failure

**B Laboratory Findings** RBC, WBC hemoglobin, packed cell volume, and sedimentation rate are normal in uncomplicated left heart failure. Polycythemia may occur in chronic cor pulmonale. Urinalysis often discloses significant proteinuria and granular casts. The BUN may be elevated because of reduced renal blood flow, but the urine specific gravity is high in the absence of primary renal disease. The serum sodium, potassium,  $\text{CO}_2$ , and chlorids are within normal limits in ordinary congestive heart failure before diuretics are used. Specific tests should be made for any suspected unusual etiologies or complications contributing to heart failure, e.g., thyrotoxicosis, bacterial endocarditis, syphilis, collagen disease, pheochromocytoma

### Differential Diagnosis.

Congestive heart failure must be differentiated from neurocirculatory asthenia, acute and chronic pulmonary disease, bronchial asthma, cirrhosis, carcinoma of the lung, nephrosis or nephritis, mediastinal tumor, repeated pulmonary emboli, obstruction of the vena cava, and anemia.

Consideration of the history together with physical findings of organic cardiovascular disease, enlarged heart, gallop rhythm, pulsus alternans, elevated venous pressure in the absence of collateral venous circulation, and prolonged circulation time differentiate congestive heart failure from these conditions.

Potentially curable causes of congestive heart failure must be specifically considered: constrictive pericarditis, mitral stenosis, pulmonary stenosis, tricuspid stenosis, subacute bacterial endocarditis, thyrotoxicosis, peripheral arteriovenous fistula, beriberi, and recent arrhythmias.

### Treatment.

The objectives of treatment are to increase the strength and efficiency of myo-

cardial contraction and to reduce the abnormal retention of sodium and water. The patient shares a significant responsibility in the management of his disease, because treatment is long-term and involves restrictions in diet and activity.

Specific search should be made for reversible noncardiac causes of failure, e.g., thyrotoxicosis, anemia, myxedema, nutritional disturbances (especially vitamin B deficiency), arteriovenous fistulas, polycythemia vera, and Paget's disease.

Determine and eliminate, if possible, the factor precipitating the cardiac failure, e.g., infection (especially respiratory), pulmonary infarction, overexertion, increased sodium intake, discontinuation of medication (especially digitalis), the onset of arrhythmia, particularly with rapid ventricular rates (e.g., atrial fibrillation), myocardial infarction, and anemia.

**A Rest** Rest in bed or sitting in a chair decreases the work of the heart and promotes sodium diuresis. Morphine- or barbiturate-induced sleep comes as a welcome relief to a patient who has spent many sleepless, dyspneic nights with his disease. Adequate rest should be maintained until compensation has occurred and then should be replaced by progressive ambulation. Most patients can use a bedside toilet with no more effort than is required for a bedpan.

Rest should be continued as long as necessary to permit the heart to regain reserve strength, but should not be so prolonged as to cause generalized debility of the patient.

Patients are usually more comfortable in a cool room.

Cardiac patients at bed rest are prone to develop phlebitis. They should be given passive or active leg exercises and an elastic stocking to prevent phlebothrombosis.

**B, Diet** At the onset of therapy, give frequent (4-6) small, bland, low-caloric, low-residue meals with vitamin supplements. The degree of sodium restriction depends upon the severity of the failure and the ease with which it can be controlled with other means. Even with the use of diuretics, unlimited sodium intake is considered unwise. Evaluation of the previous intake of sodium will provide a base-line upon which to gauge the degree of restriction required. Before drastic sodium restriction is instituted, the renal function should be evaluated to determine if the kidneys can conserve sodium. In an occasional case, 350 mg. or less of sodium may be the maximum tolerated without development of edema, although such extreme restriction is

usually necessary only when failure is first treated. Vitamin supplements may be indicated. Restricted diets and anorexia may lead to malnutrition and avitaminosis, with a superimposed beriberi type of failure.

If sodium restriction is observed faithfully, there is no indication or need for fluid restriction.

**C. Digitalis** (See p. 231.) Digitalis increases the mechanical efficiency of the heart. Increased cardiac output, decreased cardiac size and ventricular diastolic pressure, and a fall in right atrial and peripheral venous pressure follow digitalization in patients with cardiac failure. The glycosides available are qualitatively similar. They differ in speed of action, dosage, and rate of excretion. It is advisable to become familiar with a rapid I.V. and a rapid oral method. Rapid digitalization is indicated in atrial flutter and fibrillation with fast ventricular rates and in acute pulmonary edema, otherwise, slow digitalization is preferred.

#### D. Removal of Sodium and Water

1. Thiazide diuretics - Sodium diuresis is most conveniently accomplished by the use of an orally active agent such as chlorothiazide (Diuril®) or any of its analogues (see p. 237). The diuretics can be given daily or intermittently depending upon the need. Dietary or supplementary potassium must be adequate to prevent potassium depletion.

2. The mercurial diuretics (see p. 237) are slightly more potent than the thiazide diuretics. In general, they are reserved for use only when the oral preparations have been tried without success. They act by decreasing the sodium and chloride reabsorption in the renal tubules. Clinical effect is noted in about 2 hours following I.M. or subcut. injection and is essentially complete in 10-12 hours. Small quantities of mercurials (0.5-1 ml.) may result in adequate diuresis and should be used initially. They should be given in the morning so that their effect will have largely subsided by nightfall. Large doses may initiate massive diuresis with extensive fluid and electrolyte losses. This can be very distressing and can produce untoward symptoms, particularly in older people. The action of the mercurial diuretics can be potentiated by giving ammonium chloride, 2 Gm. (30 gr.) 4 times daily on the day before mercurial administration. The use of ammonium chloride for periods longer than 48 hours has no advantage and increases the danger of acidosis. Acetazolamide (Diamox®), 0.25 Gm. once or twice daily for 2-3 days before the mercurial is given, also potentiates its action.

**E. Paracentesis** Paracentesis of fluid in the chest and abdomen should be undertaken if respiration is embarrassed. Since sodium retention may occur as a result of fluid collections in the chest, abdomen, and legs, diuresis may occur following the procedure.

**F. Mechanical Measures** Venesection (in low-output failure in the absence of anemia), Southey tubes, and acupuncture may be beneficial if the more conventional forms of treatment fail. Southey tubes and acupuncture are especially valuable in severe right heart failure with obstinate dependent edema. Care must be taken to avoid a severe low-sodium syndrome with hyperkalemia.

**G. Therapeutic Myxedema** Induction of myxedema with antithyroid drugs is useful in chronic resistant left ventricular failure, resistant anginal pain, uncontrolled ventricular rate in atrial fibrillation, and in frequent recurrences of ventricular tachycardia which cannot be controlled with quinidine. It is successful in about 40% of well-chosen cases, but is a severe trial for the patient and should not be undertaken lightly. Any of the measures used to treat hyperthyroidism may be employed.

**H. Observation During Treatment of Cardiac Failure** Record the following observations on every visit:

1. Status of original symptoms.
2. New symptoms
3. Morning weight or weight with same clothes.
4. Presence of the signs of congestive failure (venous engorgement and pulsations, pulmonary rales, pleural fluid, engorgement of the liver, presence of edema)
5. Examination of the heart and blood vessels (cardiac sounds, gallop rhythm, friction rub, cardiac rhythm and apical rate, cardiac size, peripheral arterial pulsations, and status of the veins).
6. BP and presence of pulsus alternans.

#### Prognosis.

Heart failure is most often complicated by pulmonary embolization secondary to venous thrombosis occurring in the leg veins. Pulmonary infections, cardiac cirrhosis, and peripheral arterial embolization may occur. In general, the speed and adequacy of response to therapy is the most reliable guide to prognosis. Detection and removal of a precipitating condition prolongs survival. The age of the patient, the degree of cardiac enlargement, the extent of myocardial damage, and the se-

verity of underlying cardiac and associated diseases must all be considered. Survival for 5-8 years is common. Survival is longer in failure due to mitral insufficiency or that precipitated by atrial fibrillation. Survival is shorter when failure is due to mitral stenosis, syphilitic aortic insufficiency, calcific aortic stenosis, myocardial infarction, chronic pulmonary disease, and severe hypertension.

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## SPECIAL PROBLEMS IN THE MANAGEMENT OF CONGESTIVE HEART FAILURE

### Acute Pulmonary Edema

Acute pulmonary edema is a grave emergency. Treatment may vary depending upon the cause and severity. For example, in a mild attack, morphine and rest in bed alone may suffice, in an attack due to atrial fibrillation with rapid ventricular rate, lanatoside C or digoxin given I V may take precedence.

The patient should be elevated to the semi-Fowler position or placed in a chair, this decreases the venous return to the heart. Morphine sulfate, 15-30 mg. ( $\frac{1}{4}$ - $\frac{1}{2}$  gr.) I V or I M, relieves anxiety, depresses pulmonary reflexes, and induces sleep. Relief from forceful respiration decreases the negative intrathoracic pressure and the venous return to the heart.

Oxygen should be administered in high concentrations by mask or (for children) by hood or tent. Moderate concentrations (40-60%) can be achieved with an oxygen tent or nasal catheter. Oxygen relieves hypoxia and dyspnea and decreases pulmonary capillary permeability.

Positive-pressure breathing may be of great value in improving ventilation. Anti-foaming agents to lower the surface tension of the bronchial secretions may be helpful.

Soft rubber tourniquets or BP cuffs, applied with sufficient pressure to obstruct venous but not arterial flow and rotated every 15 minutes, will effectively reduce the venous return to the heart. The tourniquets should be removed gradually as the attack subsides. About 700 ml. of blood may be trapped in the extremities by this method. Venesection (300-700 ml.) is the most direct way of re-

ducing the venous return to the heart and may strikingly increase cardiac output and decrease right atrial and peripheral venous pressure in low-output cardiac failure. It is contraindicated if anemia is present.

Rapid digitalization is of great value. Extreme care should be taken in giving digitalis I V. to a previously digitalized patient. Aminophylline, 0.25-0.5 Gm. ( $\frac{1}{4}$ - $\frac{1}{2}$  gr.) slowly I V, is often helpful. It increases cardiac output, renal blood flow, glomerular filtration rate, and urine output of water and sodium. Rectal aminophylline suppositories, 0.25-0.5 Gm. ( $\frac{1}{4}$ - $\frac{1}{2}$  gr.) are often helpful and are more convenient for the patient.

In the acute recurrent pulmonary edema of hypertensive heart disease and in the presence of severe hypertension reserpine, 2.5 mg I M or I V every 8-12 hours (in addition to other measures outlined for acute hypertensive emergencies on p. 193), may be helpful. Care must be taken not to produce hypotension.

### Refractory Cardiac Failure.

When the treatment measures outlined above do not result in clinical improvement re-evaluate the total situation with particular attention to the following questions:

(1) Has bed rest been adequate? Is the patient receiving more sodium than ordered? Have treatment measures been carefully and properly administered? A review of the patient's activities, diet, and medications is essential.

(2) Are unrecognized recurrent pulmonary infarction, anemia, masked hyperthyroidism, vitamin deficiency, silent myocardial infarction, or arrhythmias present?

(3) Have complications such as acute rheumatic myocarditis or subacute bacterial endocarditis been superimposed upon a rheumatic heart?

(4) Are there electrolyte abnormalities which may have resulted from diet, mercurials and resins, if these have been used? Electrolyte disturbances may lead to mercurial resistance, produce a low-sodium syndrome, or, in the case of potassium, enhance digitalis intoxication.

### Management of Convalescence.

Provide adequate rest and exercise within tolerance. Careful attention should be paid to the treatment of noncardiac causes of cardiac failure and to the avoidance of precipitating factors.

**A Digitalization** Once digitalis is started it is usually necessary to continue it for life.



**B Low-sodium Diet** Allow 1.5 Gm. sodium chloride (600 mg of sodium) per day. It is advisable to check the patient's serum sodium or urinary sodium frequently to be certain that sodium deficiency is not occurring. An inadequate sodium intake in the presence of severe renal impairment can precipitate fatal renal failure. If thiazide compounds are used it is wise to allow the ambulatory patient at least 2 Gm. of sodium a day in his diet.

**C Diuretics** The adequately digitalized patient on a sodium-restricted diet may still accumulate edema fluid. Diuretic drugs should be added to his regimen in the amounts necessary to prevent this accumulation.

The thiazide diuretics, because of the greater convenience of oral administration, are most widely used. One of the agents listed on p. 237 can be given several times each week or even daily. Because potassium depletion is a hazard in the use of the thiazide diuretics, potassium must be added, either as potassium chloride, 1 Gm. (15 gr) t.i.d., or by the use of fruit juices.

Maintenance doses of a mercurial diuretic may be used, observing the cautions outlined on p. 219.

### Electrolyte Disturbances in Cardiac Failure.

During treatment of cardiac failure, 3 types of electrolyte disturbance may be seen

**A. Hypochloremic Alkalosis** This is due to chloride excretion out of proportion to sodium loss following mercurial diuresis, producing a low serum chloride and a high serum bicarbonate. Serum sodium and potassium levels may be normal or low. Symptoms of dehydration may be present: dry mucous membranes and loss of tissue turgor and a latent or manifest tetany.

Treatment is with ammonium chloride, 4-6 Gm. (1-1½ dr.) daily for 3-4 days, repeated after an interval of 3-4 days. Potassium salts may be given if a potassium deficit exists (see below). If tetany is present, calcium salts must be given concurrently.

Low serum sodium may be dilutional and may occur in association with hypokalemic alkalosis; administration of potassium salts such as potassium chloride may be helpful. Hypokalemic and hypochloremic alkalosis may coexist.

**B Low-sodium Syndrome** In the absence of edema, the onset of weakness, oliguria, sweating, and azotemia heralds the "low-salt syndrome." Hot weather, fever, and

vomiting are additional predisposing factors. Low serum sodium may be present without alkalosis or acidosis, or it may be complicated by dehydration and acidosis. It may follow severe sodium restriction accompanied by mercurial diuresis.

In mild cases treatment consists merely of increasing the sodium intake. For severe cases, treat with I.V. hypertonic saline.

The total body sodium is usually increased when edema is present in spite of hyponatremia. In such cases sodium should not usually be administered.

**C Hypokalemia** This may result from excessive potassium excretion due to the administration of mercurial or thiazide diuretics or acetazolamide (Diamox®) or following the administration of acid or ammonia resins to patients receiving a low-sodium diet. Hypokalemia may induce digitalis intoxication and is manifested by muscular weakness, particularly of the muscles of respiration.

Treatment consists of giving potassium chloride 3-6 Gm. (45-90 gr) daily orally, provided renal function is adequate. Caution: Parenteral potassium salts should not be given in the presence of acidosis or renal failure.

### High-Output Failure.

The term "high-output failure" means that, in the presence of fully developed congestive heart failure, the cardiac output is greater than normal but still insufficient for the needs of the body. It occurs characteristically when pre-existing heart disease is complicated by thyrotoxicosis, severe anemia (hemoglobin < 8 Gm/100 ml), pregnancy, arteriovenous fistula, beriberi, and occasionally by Paget's disease of bone, or chronic pulmonary disease or liver disease with arterial oxygen unsaturation.

The clinical picture of congestive heart failure is present except for more marked tachycardia, overactive heart, bounding pulses, and warm hands and skin generally. The circulation time may be short or normal in the face of greatly elevated venous pressure. This combination is never found in uncomplicated heart failure except when fever or one of the disorders listed above is present.

Treatment is directed at the failure as well as at the associated illness, e.g., anemia, thyrotoxicosis.

## DISEASES OF THE PERICARDIUM

### ACUTE PERICARDITIS

#### Essentials of Diagnosis

- Pleuritic or persisting substernal or precordial pain referred to the left neck, shoulder or back.
- Pericardial friction rub.
- ECG: Early concordant ST elevation, late, general symmetric T inversion without Q waves or reciprocal changes except in aVR.

Symptoms may be absent or severe pain and shock may simulate acute myocardial infarction. Rapid development of pericardial effusion may simulate congestive heart failure.

#### General Considerations.

In approximate order of frequency, infectious pericarditis is caused by viruses, *Mycobacterium tuberculosis*, pyogenic bacteria associated with bacteremia or septicemia (*pneumococcus*, *hemolytic streptococcus*, *Staphylococcus aureus*, *meningococcus*, *gonococcus*), and *brucella*. Inflammatory pericarditis includes all diseases associated with acute vasculitis, most commonly disseminated lupus erythematosus, acute rheumatic fever, and serum sickness. A miscellaneous group includes pericarditis which occurs after pericardiectomy, myocardial infarction, or trauma, pericarditis associated with uremia, metastatic tumors, and the lymphomas, and hemorrhagic pericarditis due to dissecting aneurysm.

Acute pericarditis is traditionally classified as fibrinous pericarditis or pericarditis with effusion, in which the pericardial cavity contains significant amounts of transudate, blood exudate or pus. Varying degrees of myocarditis accompany pericarditis and are responsible for the ECG changes in ST-T contours.

#### Clinical Findings.

**A Symptoms and Signs.** Acute viral pericarditis is more common in men 20-50 years of age and frequently follows a "viral" respiratory infection. The onset of pain is usually rapid or sudden, pain is precordial or substernal, pleuritic or steady (or both), and radiates to the left neck, shoulder, back, or

epigastrium. It is worse in the supine position and may be accentuated by swallowing. Tachycardia and a pericardial (often pleuro-pericardial) friction rub are present.

Fever is 37.8-39.4°C. (100-103°F.) or higher in infectious pericarditis, and is determined by the febrile pattern of the underlying disease in the other varieties.

**B Laboratory Findings.** Leukocytosis of 10-20 thousand is always present in acute viral pericarditis; leukopenia may be noted in pericarditis associated with disseminated lupus erythematosus. LE cells should be sought in isolated acute pericarditis.

**C X-ray Findings.** Chest x-rays may show cardiac dilatation, associated pneumonitis, and pleural effusion.

**D ECG Findings.** Initially, ECG changes consist only of ST-T segment elevation in all leads with preservation of normal upward concavity. Return to the base-line in a few days is followed by T wave inversion. Reciprocal changes are absent except in aVR, and Q waves do not appear.

#### Differential Diagnosis

**A Acute Myocardial Infarction.** Acute viral pericarditis usually follows a respiratory infection, occurs in the age group from 20 to 50 years, and characteristically presents with pleuritic pain. Fever, friction rub, leukocytosis and an elevated sedimentation rate are found at the onset rather than 24-72 hours later. ECG changes are usually distinctive. SGOT or LDH are only rarely elevated even in severe pericarditis.

**B Acute Pleurisy.** Pericardial friction rub is differentiated from pleural friction rub by its persistence when the breath is held, although there may also be a pleuro-pericardial friction sound which is related to respiration. ECG changes are diagnostic of pericarditis in the absence of a rub.

**C Confusion of Rub With Murmurs.** Pericardial friction rubs are differentiated by their changing character, lack of association with the usual areas of murmurs, high-pitched or "scratchy" quality, and asynchrony with the heart sounds.

#### Complications.

Pericardial effusion is the only noteworthy complication. Cardiac dilatation accompanying acute viral pericarditis rarely produces heart failure or arrhythmias.

### Treatment.

Treat the underlying condition and give analgesics as necessary for relief of pain. Salicylates and corticotropin (ACTH) or the cortisones are useful in rheumatic pericarditis.

### Prognosis.

The prognosis of viral pericarditis is usually excellent, recovery occurs in 2 weeks to 3 months, recurrences are uncommon and residual pericardial thickening or persistent ECG abnormalities are rare. The promptness and adequacy of antibiotic and surgical treatment determine the outcome in tuberculous and purulent pericarditis. Other manifestations of disseminated lupus erythematosus may become apparent after an attack of presumed "viral" pericarditis. In the miscellaneous group, the basic disorder determines the prognosis.

Spodick, D. H.: Acute Pericarditis Grune & Stratton, 1959.

Zinsser, H. F.: Idiopathic pericarditis Mod Concepts Cardiovas. Dis. 19:611-4, 1960

## PERICARDITIS WITH EFFUSION

### Essentials of Diagnosis

- Aspiration of fluid from the pericardial sac is the only infallible diagnostic procedure in pericarditis with effusion.
- Chest pain, dyspnea, weakness, distended neck veins, a large, quiet heart, and paradoxical pulse

Cardiac dilatation with congestive heart failure may be impossible to differentiate from pericarditis with effusion if pleural effusion is also present. However, rapid changes in heart size as seen by x-ray, clear lung fields with normal hilar vessels, definite paradoxical pulse, and absent cardiac pulsations on fluoroscopy are rare in congestive failure. In a patient with "heart failure," the absence of significant murmurs, arrhythmia, and hypertension should suggest pericarditis with effusion.

### General Considerations.

The most common causes of pericardial effusion are tuberculosis, malignancy, puru-

lent pericarditis, and inflammatory diseases. Rare types include chylous and "chronic idiopathic" pericarditis. Myxedema may produce significant effusion.

The speed of accumulation determines the physiologic importance of the effusion. Massive pericardial effusions, if they accumulate slowly, may produce no symptoms. However, sudden hemorrhage into the pericardium or sudden accumulation of relatively small effusions may raise the intrapericardial pressure to the point of cardiac tamponade, in which the fluid limits venous inflow and diastolic filling of the heart. In tamponade the cardiac output falls, and tachycardia and elevation of venous pressure appear as compensatory mechanisms. Shock and death may result if tamponade is not relieved.

### Clinical Findings

**A Symptoms and Signs** Pain is often absent but may be present as in acute pericarditis and as a dull, diffuse, oppressive precordial or substernal distress. Dyspnea and cough cause the patient to sit up and lean forward for relief. Dysphagia is prominent. Fever and other symptoms depend upon the primary disease (e.g., septicemia, empyema, malignancy).

The area of "cardiac" dullness is enlarged and the apex beat is not palpable or is well within the lateral border of dullness. Friction rub may persist despite a large effusion. In tamponade, distended neck veins, paradoxical pulse, and narrow pulse pressure are present. Liver enlargement, ascites, and leg edema depend upon the degree and duration of tamponade. Acute tamponade produces the clinical picture of shock.

**B Laboratory Findings** The etiology of acute effusion is determined by bacteriologic and cytologic study of aspirated fluid, of chronic effusion, by pericardial biopsy. Leukocytosis and a rapid sedimentation rate are present when the effusion is infectious or inflammatory. The arm-to-tongue circulation time is normal in the presence of large effusion without tamponade, this is often a clue to the correct interpretation of a "large heart shadow" on chest x-ray. In myxedema, pericardial effusion and prolongation of the circulation time are present without tamponade.

**C. X-ray Findings** A rapidly enlarging "cardiac" silhouette with sharply defined margins, an acute right cardiophrenic angle, clear lung fields, and pleural effusion are common. Cardiac pulsations are feeble or absent.

1 V.  $\text{CO}_2$  administration allows estimation of the distance between the atrial cavity and the pericardial sac by x-ray.

D. ECG Findings T waves are low, flat, diphasic, or inverted in all leads, QRS voltage is uniformly low.

#### Complications.

Cardiac tamponade is a serious complication. Rapidly developing pericardial effusions or hemorrhage into the pericardial sac may so impede venous return and cardiac filling that cardiac output falls and irreversible shock occurs.

Purulent pericarditis is usually secondary to other infection elsewhere but is at times caused by contamination of a previous pericardial tap.

#### Treatment.

A. Emergency Treatment (Paracentesis) The indications for pericardial paracentesis are the symptoms and signs of cardiac tamponade. As the pericardial fluid increases in amount and particularly when it increases rapidly, the venous pressures may rise considerably and the cardiac output may progressively fall. When this occurs the patient becomes weak, pale, and dyspneic, and the pulse pressure becomes very narrow and the pulse rapid and thready. If, in the meantime, the patient goes into shock. Under these circumstances removal of the pericardial fluid may be life-saving, the fluid should be removed slowly to avoid cardiac dilatation or severe responses to cardiac reflexes.

1. Sites of puncture - (Caution. Avoid puncture of the ventricular muscle.) Puncture may be made at the left fifth or sixth interspace about 1 cm (3/8 inch) within the area of cardiac dullness or 1-2 cm. (3/8-3/4 inch) inside the left heart border as localized by x-ray [roughly 7-8 cm (23/4-3 1/8 inches) outside the left sternal line]. The needle is pushed slowly inward and slightly upward. If effusion is present, one should find fluid within 3-5 cm (1 1/4-2 inches) [at times, 7-8 cm (23/4-3 1/8 inches)]. Puncture may also be made in the epigastric area between the xiphoid process and the left sternal margin. Insert the needle upward at an angle of about 30°, pointed toward the midline. The pericardium is reached at about 3-4 cm (1 1/4-1 1/2 inches). The posterior approach is to be used, as a rule, only when the above approaches are unsuccessful, it rarely is used if one suspects a purulent pericarditis. Enter the seventh or eighth interspace in the midscapular line. The left

arm is elevated to rotate the scapula out of the way. The needle is directed inward and medially.

2. Equipment - No. 16 or 18 needle with short bevel and fitting stylet, No. 26 or 27 needle to infiltrate the skin with procaine and a 20-30 ml syringe to remove fluid. The syringe should be connected to the needle with a four-inch piece of rubber tubing to prevent excessive movement of the needle.

3. Technic - Clean and sterilize skin over the area to be punctured. Drape the surrounding area with sterile towels. Infiltrate the skin with 1-2% procaine solution. Insert the needle (detached from the syringe and without a stylet) slowly into the skin following the directions according to the site selected. When the fluid is encountered it must be withdrawn very slowly. Sudden withdrawal may result in acute cardiac dilatation, failure, or death. Some consider it advisable to replace half the amount of fluid withdrawn with air, both to prevent excessive dilatation and to give better visualization by x-ray. With the needle in place remove 20 ml. portions after the withdrawal of each portion, inject 10 ml. of air.

After the needle is removed, a simple dressing over the needle puncture is adequate.

#### B. Specific Measures

1. Tuberculous pericarditis - The current treatment is to treat the systemic infection with bed rest, attention to nutrition and other general factors, and intensive antituberculous chemotherapy. If fever and signs of pericardial effusion do not rapidly subside and are still obvious in one month, surgical decortication of the pericardium should be considered in order to prevent chronic constrictive pericarditis. Good judgement is required to determine when the disease is progressing despite medical treatment and when signs of constriction are appearing.

2. Rheumatic pericarditis with effusion - Treat as for rheumatic fever. The salicylates may help in causing fluid resorption. Paracentesis is usually unnecessary but should be performed if tamponade occurs.

3. Hydropericardium due to heart failure - Treatment of the congestive failure is usually sufficient.

4. Hemopericardium due to rupture of adjacent structure (usually post-traumatic) - If fluid accumulation is excessive, remove fluid at once.

5. Treat infection with appropriate chemotherapeutic agents and perform paracentesis as needed to relieve pressure. When fluid is being removed instill 50,000-150,000 units of

penicillin or the equivalent topical amount of streptomycin or other indicated antibiotic into the pericardial sac, and repeat whenever a tap is performed. Chemotherapeutic agents should be continued as long as purulent effusion is present. If fluid is encapsulated or the patient is not responding to therapy, surgical drainage via pericardiotomy may be necessary.

#### Prognosis.

Tuberculous pericarditis causes death in the majority of untreated cases and results in chronic constrictive pericarditis in many that survive. The mortality rate is very low with early and adequate treatment, the long-term effect on the incidence of constrictive pericarditis is not known.

Acute benign pericarditis is rarely fatal.

Rheumatic pericarditis, if severe and protracted, is associated with myocarditis, and this determines the immediate prognosis. Residual pericardial disease of clinical significance does not occur.

Purulent pericarditis, since it is usually associated with a blood stream infection or infection elsewhere is usually fatal if not treated, however, it responds satisfactorily to antibiotics.

Evans, J.M., & C.W. Walter: Alterations in the circulation during cardiac tamponade due to pericardial effusion. *Am Heart J* 39:181-7, 1950.

Scheuer, J.: Chronic idiopathic pericardial effusion: with special reference to the development of constrictive pericarditis. *Circulation* 21:41-8, 1960.

## CHRONIC CONSTRICTIVE PERICARDITIS

#### Essentials of Diagnosis

- Markedly elevated venous pressure.
- Slight to moderate cardiac enlargement and quiet heart action.
- Paradoxical pulse.
- Signs of advanced right heart failure.

Marked venous engorgement in the neck without systolic pulsation, slight to moderate cardiac enlargement, absence of significant murmurs or hypertension, paradoxical pulse, and ECG changes distinguish chronic constrictive pericarditis from tricuspid stenosis, congestive heart failure, cirrhosis of the liver, mediastinal tumor,

nephrosis, and obstruction of the vena cava.

#### General Considerations.

Encasement of the myocardium by an adherent, dense fibrous pericardium may be asymptomatic or may prevent ventricular expansion during diastole. If this happens the stroke volume is low and fixed and cardiac output can be increased only by tachycardia. Venous pressure rises as in congestive heart failure, and this, together with renal retention of sodium and water, produces the peripheral signs of right heart failure.

#### Clinical Findings.

**A. Symptoms and Signs** The principal symptoms are slowly progressive dyspnea, fatigue, and weakness on exertion, abdominal distention, and leg edema. Examination shows markedly distended neck veins with weak or absent systolic pulsations but prominent diastolic retraction, a moderately enlarged heart with a quiet precordium in the presence of tachycardia, faint heart sounds, a low pulse pressure with a high diastolic level, paradoxical pulse, enlarged liver, ascites, and edema of both legs and the scrotum. Atrial fibrillation is frequently present.

**B. Laboratory Findings** The arm-to-tongue circulation time is prolonged. Rarely, tuberculous infection of the lungs or other organ is noted.

**C. X-ray and Fluoroscopic Findings** The "heart" is usually moderately enlarged. Its shape is not consistent with valvular or hypertensive heart disease. Pulsations are weak or absent. Lung fields are clear. Pericardial calcification is very common but is not diagnostic of constrictive pericarditis.

**D. ECG Findings** T waves are flat or inverted, low voltage of QRS complexes is variable. Atrial fibrillation is common.

#### Complications.

In cases of tuberculous origin, a miliary spread or acute flare-up of the intrapericardial infection may occur.

Thrombophlebitis of the leg veins may occur secondary to elevated venous pressure, venous stasis, and inactivity.

#### Treatment.

Give a low-sodium diet and diuretics (with or without intermittent ammonium chloride as in cardiac failure) to combat ascites and congestive failure. Digitalis is usually of little value.

Surgical removal of the constricting pericardium can frequently restore a patient to normal health. If congestive phenomena are chronic or the pericarditis is progressive, surgical intervention is the only method offering possible cure.

#### Prognosis.

Constrictive pericarditis known to be due to tuberculosis is usually fatal without anti-tuberculosis drugs and surgery. Most patients with constrictive pericarditis due to any cause have increasing disability because of ascites and edema and die of mechanical "heart failure." A few patients show no progression of symptoms or signs for years. Spontaneous regression is rare.

Detering, R A., & A H Humphreys, II.

Factors in the etiology of constrictive pericarditis. *Circulation* 12 30-43, 1955

Sawyer, C.G., & others. Chronic constrictive pericarditis: further consideration of the pathologic physiology of the disease. *Am Heart J* 44:207-30, 1952

## DISEASES OF THE MYOCARDIUM

### CHRONIC PULMONARY HEART DISEASE (Chronic Cor Pulmonale)

#### Essentials of Diagnosis

- Symptoms and signs of chronic bronchitis and pulmonary emphysema.
- No significant murmurs or hypertension.
- ECG: tall peaked P waves and right axis deviation.
- Chest x-ray: enlarged right ventricle, pulmonary conus and artery.

Respiratory complaints of many years' duration, the relative absence of orthopnea, and the presence of cyanosis and clubbing differentiate chronic cor pulmonale from other forms of heart failure.

#### General Considerations.

Cor pulmonale refers to the right ventricular hypertrophy and eventual failure resulting from pulmonary parenchymal or vascular

disease. It may be acute, subacute, or, most commonly, chronic, and its clinical features depend both upon the primary disease and its effects on the heart. (See also p. 155.)

Chronic cor pulmonale is most commonly caused by chronic obstructive pulmonary emphysema, often referred to as "chronic asthmatic bronchitis." Less common or rare causes include pneumoconiosis, pulmonary fibrosis, kyphoscoliosis, primary pulmonary hypertension, and repeated episodes of sub-clinical pulmonary embolization. Emphysema and associated fibrosis result in obliteration of capillaries and disturbance of pulmonary function with resultant hypoxia. Compensatory polycythemia and increased cardiac output also appear. The combined effect of these changes is increased pulmonary artery pressure, which in turn leads to right ventricular hypertrophy and eventual failure of the "high output" variety.

#### Clinical Findings.

**A. Symptoms and Signs.** The dominant symptoms of compensated cor pulmonale are respiratory in origin: chronic productive cough, exertional dyspnea, wheezing respirations, undue fatigability, and weakness. When the pulmonary disease has advanced sufficiently to cause right ventricular failure, these symptoms are intensified. In addition, dependent edema, right upper quadrant pain, and digestive disturbances may appear. Signs include cyanosis, clubbing, distended neck veins, pulmonary emphysema, prominent lower sternal or epigastric pulsations, an enlarged tender liver, and dependent edema. The heart size cannot be determined because of emphysema but there is no evidence of valvular disease. Pulses are full and the extremities warm unless the patient is terminal or in shock.

**B. Laboratory Findings.** Polycythemia is usually present in cor pulmonale secondary to emphysema. The arterial oxygen saturation is below 85%,  $pCO_2$  is often elevated. Venous pressure is significantly elevated in right ventricular failure, but the circulation time may be normal or only slightly prolonged.

**C. ECG Findings.** The ECG shows right axis deviation, peaked P waves. Frank right ventricular hypertrophy is uncommon except in "primary pulmonary hypertension," in which this is the rule.

**D. X-ray Findings.** Chest x-ray discloses the presence or absence of parenchymal disease and a prominent or enlarged right ventricle, pulmonary conus, and artery.

### Complications.

Intercurrent respiratory infections increase dyspnea, cough, and cyanosis and may precipitate a dangerous degree of respiratory acidosis in advanced emphysema. Neurologic manifestations of CO<sub>2</sub> narcosis may appear delirioration, somnolence, coma, and occasionally convulsions.

### Differential Diagnosis.

In its early stages cor pulmonale can be diagnosed only on x-ray or ECG evidence. When frank congestive signs appear, differentiation from primary left ventricular failure is possible by considering the predominant history of respiratory complaints, the absence of orthopnea, the degree of cyanosis, bounding pulses, and warm extremities in the presence of edema. ECG demonstration of right axis deviation, normal or only moderately prolonged circulation time, and absence of demonstrable factors pointing to left failure are helpful.

### Treatment.

**A. Specific Measures** Give appropriate antibiotic therapy for the respiratory infection that so commonly precedes failure in this type of case. The patient may be afebrile.

### B. General Measures

1. Intermittent positive-pressure mask breathing, e.g., with the Bennett, Emerson, Bird, or similar respirator, at pressure settings of +10 to +15 (inspiration) may be helpful. Patients who do not breathe spontaneously may be treated advantageously with the automatic Bird respirator, the other nonautomatic apparatuses may be operated manually. These devices provide a convenient, effective method of administering bronchial dilators, antifoaming agents, and aerosols (see p. 167). None of the intermittent devices controlled by the patient lower the cardiac output.

2. In cor pulmonale, intermittent positive-pressure breathing, especially when combined with effective bronchial dilators, is probably the most effective therapeutic measure. The use of mechanical devices in acute respiratory distress may not be helpful and should perhaps be postponed until other measures have improved the situation.

3. CNS depressants, especially narcotics, barbiturates, and hypnotics are strongly contraindicated in the treatment of cardiac failure secondary to primary pulmonary disease (cor pulmonale) due to their marked depressant action on the respiratory centers.

4. Treat heart failure in the usual way with bed rest, restriction of sodium, diuretics,

and digitalis. Digitalis may not be effective if cardiac output is high.

5. Give acetazolamide (Diamox®) 250 mg. after adequate ventilation has been restored, i.e., when CO<sub>2</sub> elimination is effective.

### Prognosis

Compensated cor pulmonale has the same outlook as the underlying pulmonary disease. Once congestive signs appear, the average life expectancy is 1-2 years, but survival is significantly longer when uncomplicated emphysema is the cause. Left ventricular failure secondary to coronary artery disease, hypertension, or aortic valve lesions may develop and shorten expectancy accordingly.

## SYPHILITIC HEART DISEASE

### Essentials of Diagnosis

- Heavy linear calcification or localized dilatation of the ascending aorta on x-ray
- Aortic valvular insufficiency without stenosis or mitral valve disease.
- Evidence of syphilitic etiology: history of infection, positive STS, or presence of other forms of late syphilis.

The clinical picture can mimic rheumatic and arteriosclerotic heart disease. Syphilitic aneurysms are indistinguishable from those caused by arteriosclerosis.

### General Considerations.

Syphilitic "heart disease" may consist of aortic valvular insufficiency (most common), aortic dilatation or aneurysm, or narrowing of the coronary ostia. It comprises less than 5% of all heart disease in population groups which have ready access to effective treatment of syphilis. It is more common in men (3:1) and is usually diagnosed between the ages of 35 and 55 (10-20 years after the primary infection). STS are positive in about 85% of untreated cases. The ascending aorta, arch, and descending aorta are most commonly affected, the abdominal aorta is rarely involved. Aortic valve insufficiency occurs in about 10% of cases of untreated syphilitic aortitis. One or both of the coronary ostia may be partially occluded.

### Clinical Findings.

**A. Aortitis** There are no symptoms, and physical signs are absent unless dilatation has

occurred in a man under the age of 40 with out hypertension or demonstrable arterio sclerosis a ringing or accentuated second aortic sound with or without a soft aortic systolic murmur is suggestive of syphilitic aortitis. Fluoroscopic evidence of increased width and pulsation of the ascending aorta best seen in the left anterior oblique view in the absence of elongation is also suggestive. Heavy linear calcification limited to the root of the aorta and arch is almost diagnostic.

**B Aortic Insufficiency** Clinical x ray and ECG manifestations are as for rheumatic aortic insufficiency. Ten per cent of cases are associated with saccular aneurysm. Aortic insufficiency may produce no symptoms for surprisingly long periods once heart failure develops however it soon becomes refractory to treatment and death usually occurs within 6 months to 2 years.

**C Aortic Aneurysm** Symptoms and signs are dependent upon the site and size of the aneurysm. Aneurysm of the ascending aorta is characterized by visible pulsation or dullness of the manubrium and in the first to third interspaces parasternally. Lowered BP in the right arm and an aortic systolic murmur and thrill without peripheral signs of aortic stenosis. Aneurysm of the aortic arch is characterized by cough, dyspnea and recurrent pulmonary infections (compression of trachea or right main stem bronchus), hoarseness (compression of recurrent laryngeal nerve), edema of the face and neck, distended neck veins and prominent veins over upper chest (compression of superior vena cava) and dysphagia (compression of the esophagus). Aneurysm of the descending aorta is usually asymptomatic when it is large it may erode the ribs or spine producing pain which is worse in recumbency and visible or palpable pulsations medial to the left scapula.

X ray findings consist of saccular or sharply defined fusiform bulging of the thoracic aorta with increased pulsation. Clot formation or periaortic fibrosis may dampen the pulsations and simulate a solid tumor. Retrograde or I V injection of Iodopyracet (Diodrast®) differentiates the 2 by demonstrating continuity of the aorta with the lumen of the aneurysm.

**D Narrowing of the Coronary Artery Ostia** The manifestations are identical with those of arteriosclerotic coronary artery disease. Its syphilitic origin can only be inferred in the presence of one of the other manifestations of syphilitic aortitis.

## Treatment

**A Specific Measures** Treat latent syphilis as outlined in Chapter 21. Several subsequent courses of penicillin are advised by some authorities at intervals of 6 months or one year especially if the STS remains positive.

**B General Measures** Bed rest is desirable during treatment with penicillin.

**C Surgical Measures** Surgical repair of the aneurysm has been attempted but is hazardous.

## Complications

**A Aortic Insufficiency** Left ventricular hypertrophy which may progress to failure.

**B Aortic Aneurysm** Recurrent pulmonary infection, bronchiectasis, atelectasis, bronchial hemorrhage and rupture.

## Prognosis

**A Aortitis** Ten to 20% of patients develop aortic insufficiency and other manifestations of syphilitic cardiovascular disease. In the remainder life expectancy is not affected.

**B Aortic Insufficiency** If penicillin is given when the signs of aortic insufficiency are purely auscultatory the progress of the lesion may be slowed or even arrested; this significantly improves the prognosis for survival.

**C Aortic Aneurysm** Once aneurysms have reached sufficient size to produce symptoms by compression of adjacent structures life expectancy is measured in months. Longer survival is possible when the aneurysm is small and effective therapy for syphilis has been given. Death is usually due to rupture of the aneurysm.

**D Narrowing of the Coronary Artery Ostia** This condition tends to aggravate the heart failure due to syphilitic aortic insufficiency and predisposes to sudden death.

- MacFarlane W V, Swan W G & R E Irvine. Cardiovascular disease in syphilis. A review of 1330 patients. *Brit M J* 1 827 32 1956.
- Rimsa A & G C Griffith. Trends in cardiovascular syphilis. *Ann Int Med* 46 915 24 1957.



## ACUTE MYOCARDITIS & ENDOMYOCARDIAL DISEASES

### Essentials of Diagnosis.

- Persistent tachycardia, low systolic BP, diminished first heart sound, changing systolic murmurs, gallop rhythm, pulsus alternans, prominent "right heart" failure,
- Absence of recognizable common etiology of heart failure.
- ECG Atrioventricular or intraventricular conduction defect, abnormal T waves, low voltage QRS, no characteristic pattern,

*Myocarditis and endomyocardial disorders vary so much in clinical signs that they are confused with thyrotoxicosis, bacterial endocarditis, "painless" coronary artery disease, rheumatic heart disease with faint or atypical murmurs, pericardial tamponade, and neoplastic disease of the heart. Sinus tachycardia and minor ECG changes are an insufficient basis for diagnosis.*

### General Considerations.

Acute myocarditis is a focal or diffuse inflammation of the myocardium occurring during or after many viral, bacterial, rickettsial, spirochetal, fungal, and parasitic diseases. Mild forms are very common and are recognizable only by serial ECG changes. Severe myocarditis producing signs and symptoms occurs most commonly in acute rheumatic fever, diphtheria, scrub typhus, and Chagas' disease (Trypanosoma cruzi infection). Bacteremia, viral pneumonia and encephalitis, and trichinosis may be associated with myocarditis of varying severity.

Endomyocardial disease includes a wide variety of noninfectious myocardial diseases whose clinical manifestations are similar to those of myocarditis except that fever, peripheral embolization, and refractory heart failure are more common. A partial list of these include Fiedler's isolated myocarditis, subendocardial fibroelastosis, idiopathic cardiac hypertrophy (congenital and adult), familial cardiomegaly, idiopathic myocardial failure in pregnancy, collagen diseases (scleroderma, disseminated lupus erythematosus, polyarteritis nodosa, serum sickness), and amyloidosis.

### Clinical Findings.

**A. Symptoms and Signs** Mild forms of myocarditis are asymptomatic and are overshadowed by the underlying disease. Severe myocarditis may result in weakness, syncope, dizziness, dyspnea, nausea, vomiting, chest pain, and shock or sudden death. In endomyocardial diseases the course may be acute, subacute, or chronic, but the symptoms are similar. Fiedler's myocarditis, idiopathic cardiac hypertrophy, and idiopathic heart failure of pregnancy are characterized by fever, peripheral emboli, and heart failure. Noncardiac manifestations of the basic disease may be noted, as in carcinoid syndrome, Friedreich's ataxia, and the collagen diseases.

*In addition to those of the underlying disease (e.g., hemochromatosis, scleroderma), signs include fever, tachycardia, cardiac enlargement, faint heart sounds, changing systolic murmurs, arrhythmias, variable congestive heart failure (predominantly right-sided), with hepatomegaly, gallop rhythm, pulsus alternans, and distended neck veins, and signs of cerebral or peripheral embolization.*

**B. ECG Findings** Partial to complete atrioventricular block and intraventricular conduction defects diffusely flat to inverted T waves, and low voltage QRS. In mild myocarditis, only transient flattening or inversion of T waves may be noted.

### Treatment.

No specific therapy is available. Steroids are occasionally helpful in the collagen group of diseases. The general principles of treatment of cardiac failure and anemia are to be followed as they apply in specific cases.

### Prognosis

**A. Acute Myocarditis** The common forms rarely produce disability or death. The overall mortality rate in diphtheritic myocarditis is 25%, the death rate approaches 100% if shock or congestive heart failure occurs and is 50-75% with complete heart block. Mortality is similarly high in Chagas' disease. Myocarditis is the chief cause of death in scrub typhus. With the exception of rheumatic fever, there are no late sequelae after recovery.

**B. Endomyocardial Diseases** Death may occur in a few days, as in Fiedler's myocarditis; or cardiac disability may be rare, as in Friedreich's ataxia. The disease is generally fatal within a few weeks to a few months (occasionally longer) in Fiedler's myocarditis, subendocardial fibrosis, idio-

pathic hypertrophy and amyloidosis. Complete recovery is possible in endomyocardial nutritional disorders and those associated with pregnancy.

Fowler N O Gueron M & D T Rowlands Jr Primary myocardial disease. *Circulation* 23 498 508 1961

Mattingly T W Clinical features and diagnosis of primary myocardial disease. *Mod Concepts Cardiovas Dis* 30 677 82 and 683 6 1961

## THE CARDIAC PATIENT & SURGERY

Surgery in the cardiac patient is inevitably more hazardous than in patients with normal hearts. When shock, hemorrhage, hypoxia, struggling during induction, thromboembolism, and hypoventilation occur in a patient with heart disease, the danger of coronary occlusion, myocardial infarction, cardiac failure, and arrhythmias is increased.

The major cardiac lesions which increase the risks of surgery are rheumatic heart disease (especially aortic stenosis), coronary artery disease (about 5% additional hazard), and syphilitic cardiovascular disease, especially if there is involvement of the coronary ostia (as suggested by associated angina). Hypertension without cardiac or renal involvement does not usually add to the surgical risk.

If possible, surgery in patients with recent congestive failure should be delayed 3 weeks after recovery. In patients with recent myocardial infarction, a delay of 3-6 months is advisable. The patient should be brought into the best cardiac state possible before surgery, with medications, diet, and vitamin supplements. Anemia should be corrected. Pre-surgical electrolyte management is also very important in the cardiac patient.

In inducing and maintaining anesthesia in a cardiac patient, adequate ventilation, oxygenation, and smooth induction without struggling are important.

During surgery, hypotension should be treated promptly if it occurs. Anemia should be avoided, and fluid therapy should be given to maintain optimal cardiac reserve.

## THE CARDIAC PATIENT & PREGNANCY

The following information will assist in estimating the likelihood of cardiac failure in a pregnant woman: (1) Functional class before pregnancy, (2) the age of the patient, (3) the size of the heart, (4) the structural lesion of the heart, (5) the presence of arrhythmias, (6) the patient's socioeconomic status (e.g., if children are at home or if the patient must work), (7) the intelligence and cooperation of the patient, and (8) the presence of associated disease.

### Assessment of Risk of Heart Disease in Pregnancy

**A Little or No Functional Incapacity.** All most all patients who are asymptomatic or who have only mild symptoms with ordinary activities can continue to term under close medical supervision. If the patient develops more severe symptoms with activity, she should be hospitalized, treated for failure, and kept in bed until term.

**B Moderate or Marked Functional Incapacity.** If the patient has pure mitral stenosis and develops acute pulmonary edema or has moderate to marked symptoms with activity, mitral valvulotomy should be considered. This has been successfully accomplished up to the eighth month. If the patient does not have an operable lesion, she should be hospitalized, treated for cardiac failure, and kept in bed until term.

**C Very Marked Functional Incapacity.** All patients seen during the first trimester who have symptoms on little or no activity and who do not have an operable cardiac lesion should be aborted, because of the high incidence of recurrent failure and death in this group of patients.

### Physiologic Load Which Pregnancy Imposes on the Heart

The work of the heart increases by about 50% at the beginning of about the third month when the blood volume and cardiac output increase. The placenta acts as an arteriovenous fistula. Cardiac failure may occur at any time from the end of the first trimester up to 2-3 weeks before term, at which time the load for some unaccountable reason decreases.

Sodium should be restricted after the second month.

### Management of Labor.

Current opinion holds that vaginal delivery is to be preferred except when there is an obstetric indication for cesarean section. Coarctation of the aorta may be the only cardiac disease which contraindicates vaginal delivery, because of the danger of rupture of the aorta.

The second stage should be made as short as possible, using forceps when possible. Ergonovine meslate (Ergotrate<sup>®</sup>) should probably not be used because of the increased work of the heart which it causes.

## CARDIOVASCULAR DRUGS

### DIGITALIS & DIGITALIS-LIKE PREPARATIONS

#### Action of Digitalis & Digitalis-like Preparations.

A. In congestive failure digitalis increases the force of contraction of the myocardium and the efficiency of the heart. Digitalis significantly increases cardiac output, decreases right atrial pressure, decreases the venous pressure, and increases excretion of sodium and water and so corrects some of the hemodynamic and metabolic alterations of cardiac failure.

B. Digitalis slows conduction between the atrium and the ventricle and depresses the sino-atrial and atrioventricular nodes, both by direct action (late) and by reflex stimulation of the vagus nerve (early).

C. Digitalis prolongs the refractory period of the atrioventricular node and therefore, in the presence of a rapid atrial rate or atrial fibrillation, is able to reduce the ventricular rate by reducing the number of atrial impulses to which the ventricle can respond.

D. Digitalis increases the ability of the ventricular muscle to initiate impulses.

#### Principles of Administration.

A. Digitalis Saturation (Digitalization) Digitalis must be administered initially in large doses to achieve tissue saturation and produce a therapeutic effect. Smaller doses (representing the amount metabolized and excreted) are administered daily thereafter as long as the indications for digitalis persist (usually for life).

B. Criteria of Adequate Digitalization Digitalis is administered until a therapeutic effect has been obtained (e.g., relief of congestive failure or slowing of the ventricular rate in atrial fibrillation), or until the earliest toxic effect (anorexia) appears.

1. In congestive failure with normal rhythm - Digitalization is adequate if (1) diuretic action is adequate, and edema fluid is lost, (2) cardiac size is decreased as dilatation becomes less, (3) venous pressure and circulation time return to normal, (4) the heart rate decreases (if increase was due to failure), (5) an engorged tender liver becomes smaller and nontender.

2. In atrial fibrillation - When the rate is below 80 after exercise, one can usually consider the patient adequately digitalized. Exercise consists of requiring bed patients to sit up 5 times and ambulatory patients to hop up and down on one foot 5 times.

C. ECG Effects The most characteristic change which digitalis produces in the ECG is sagging of the ST segment and displacement of the T waves in a direction opposite to that of the main deflection. Later the P-R interval may be prolonged. The ST-T changes cannot be used as criteria of digitalis toxicity, for the effects appear before saturation is present and persist for 2-3 weeks after digitalis has been discontinued. However, the ECG is often of value in determining whether digitalis has been administered in the past 2-3 weeks and may give an idea of the amount.

D. Toxic Effects of Digitalis There are no nontoxic digitalis preparations, and the difference between the therapeutic and toxic level is very small.

1. Slight toxicity - Anorexia, ventricular ectopic beats.

2. Moderate toxicity - Nausea and vomiting, headache, malaise.

3. Severe toxicity - Diarrhea, blurring of vision, confusion, disorientation.

4. Extreme toxicity - Abdominal pain, high-degree conduction blocks, and atrial or ventricular fibrillation.

E. Relationship of Digitalis to Potassium Ion There is an antagonism between potassium and digitalis, and digitalis toxicity is more likely to occur in any clinical situation in which potassium is decreased in the cells or serum, e.g., as a result of potassium diuresis due to mercurial or thiazide diuretics, or following cortisone therapy. In these circumstances, potassium ion should be given.

## Digitalls &amp; Digitalis like Preparations

	Glycoside and Preparations Available	Dose		Method of Administration	Speed of Maximum Action and Duration
		Digitalizing	Maintenance		
PARENTERAL	Ouabain 1 ml and 2 ml ampules 0.25 mg (1/240 gr)	0.25 0.5 mg (1/240 1/120 gr)	Not used for maintenance	0.25 0.5 mg (1 2 ml) diluted in 10 ml saline slowly I V follow with another drug (see below)	1/2 1 1/2 hours duration 2 4 days
	Deslanoside (Cedilanid D <sup>®</sup> ) 2 ml and 4 ml ampules 0.4 and 0.8 mg	8 ml (1.6 mg)	0.2 0.4 mg (1 2 ml)	1.2 mg (6 ml) I V or I M and follow with 0.2 0.4 mg (1 2 ml) I V or I M q 3 4 hours until effect is obtained	1 2 hours duration 3 6 days
	Digitoxin (dilute before use) 1 ml and 2 ml ampules 0.2 and 0.4 mg	1.2 mg (6 ml)	0.05 0.2 mg	0.6 mg (3 ml) I V or I M followed by 0.2 0.4 mg q 4 6 hours until 1.2 mg is given	3 8 hours duration 14 21 days
	Digoxin (dilute before use) 1 ml ampules 0.5 mg	1.5 mg (3 ml)	0.25 0.75 mg (0.5 1.5 ml)	1 mg (2 ml) I V and 0.5 mg (1 ml) in 3 4 hours then 0.25 mg (0.5 ml) q 3 4 hours until effect is obtained	1 2 hours duration 3 6 days
	Digitalis 0.03 0.06 and 0.1 Gm tablets (1/2 1 and 1 1/2 gr)	1 1.5 Gm (15 22 1/2 gr)	0.05 0.2 Gm (3/4 3 gr)	0.6 Gm (10 gr) at once 0.4 Gm (6 gr) in 6 8 hours 0.2 Gm (3 gr) q 6 hours for 2 3 doses then 0.1 Gm (1 1/2 gr) b i d until effect is obtained	6 8 hours duration 18 21 days
ORAL	Digitoxin 0.1 0.15 and 0.2 mg tablets	1.2 mg	0.05 0.2 mg	0.6 mg at once and repeat in 12 hours and then 0.2 mg b i d until effect is obtained	6 8 hours duration 14 21 days
	Digoxin 0.25 and 0.5 mg tablets	2 3 mg	0.15 0.50 mg	1 mg at once and then 0.5 0.75 mg q 6 hours Total 3 mg	4 6 hours duration 2 6 days
	Lanatoside C (Cedilanid <sup>®</sup> ) 0.5 mg tablets	7.5 mg	0.5 2.5 mg	3.5 mg at once 1 mg in 6 hours then 0.5 mg q 6 hours until effect is obtained	
	Acetyldigitoxin (Acylianid <sup>®</sup> ) 0.1 and 0.2 mg tablets	1.6 2.2 mg	0.25 1 mg	2 mg in 24 hours or 0.6 1 mg daily until effect is obtained	4 6 hours duration 14 21 days
	Gitalin (Gitaligin <sup>®</sup> ) 0.5 mg tablets	6.5 8 mg	0.1 0.2 mg	1 mg t i d until effect is obtained	4 6 hours duration 6 14 days

**F Treatment of Severe Digitalls Toxicity**  
 Withhold digitalls and diuretics until the manifestations of toxicity have subsided and treat the cardiac failure. If present with other means. Give potassium salts 4.8 Gm (60 120 gr) orally per day in divided doses or depending upon the clinical urgency well diluted I V potassium salts slowly (not more than 10 20 mEq/hour). In emergency circumstances potassium may be given more rapidly under ECG control.

The differentiation of digitalls toxicity and inadequate digitalization is sometimes quite difficult. The only safe procedure if uncer-

tain is to withhold digitalls and diuretics and treat the cardiac failure with restriction of sodium and other means to improve cardiac function. Nausea vomiting and arrhythmias which are in fact due to digitalls toxicity will subside in 2 3 days. Caution. Do not give rapid acting I V digitalls preparations to a patient taking digitalls who is apparently in failure unless it is certain that the manifestations observed are not due to digitalls toxicity.

**G Choice of Digitalls Preparation** (See chart above). All of the cardiac glycosides

have similar pharmacologic properties differing only in dose, speed of onset of action and duration of action. With digitalis leaf and digitoxin there is a long latent period before maximal effect is achieved, and the duration of effect is long. Digoxin (Lanoxin®), lanatoside C (Cediland®) and deslanoside (Cedilanid D®) have a much more rapid onset of action and briefer duration of effect. Acetyldigoxin (Acyland®) is recommended only for oral administration and is equivalent to digoxin. Gitalin (Gitalgin®) has properties intermediate between those of digitoxin and digoxin. Ouabain exerts its effect within a few minutes but it is rarely used in the U.S. because other parenteral glycosides are available.

#### Indications for Administration of Digitalis

A Cardiac failure (left, right or combined) with sinus rhythm or atrial fibrillation

B Atrial fibrillation or flutter with a rapid ventricular rate

C Supraventricular paroxysmal tachycardia

D Before cardiac surgery, especially mitral valvulotomy, in patients with sinus rhythm so that if paroxysmal atrial fibrillation occurs during or following surgery the ventricular rate will not be too rapid.

E Prevention of paroxysmal atrial arrhythmias in patients in whom quinidine has failed or cannot be tolerated.

#### Routes of Administration of Digitalis

##### A Parenteral Administration

1 Emergency digitalization (1) Acute pulmonary edema or other severe failure. Caution should be used in giving the full digitalizing dose in a single injection I.V. under these circumstances. The drug should be given slowly in divided doses. (2) Treatment of atrial arrhythmias when the need for control of the ventricular rate is urgent.

2 Inability to take digitalis orally, e.g. in nausea and vomiting due to any cause, in coma and postoperatively.

B Oral administration is used whenever parenteral administration is not indicated.

#### Methods of Digitalization

A Untreated Cases (When the patient has received no digitalis in the preceding 2 weeks.)

1 Parenteral digitalization. Caution. Never administer a full digitalizing dose I.V. unless it is certain that no digitalis has been

given in the preceding 2 weeks. Always give I.V. preparations slowly.

Select the drug on the basis of the rapidity of effect needed. Except in extreme emergencies do not give the entire average digitalizing dose in a single dose. A good general rule is to give one-half to two-thirds of the average digitalizing dose immediately and then give the remainder in 2-4 hours. Observe carefully for digitalis toxicity. When the initial dose is given parenterally, it is advisable to give also an average maintenance dose of a digitalis preparation if the patient is able to swallow. Optimal digitalization can thus be achieved and maintained from the start. It is not necessary to give the same glycoside orally that was used for the initial medication (e.g. may digitalize with I.V. lanatoside C and give digitalis leaf for maintenance).

A history of digitalis therapy is often difficult to obtain, and digitalis toxicity has occurred in patients who have denied or were unaware of having received the drug. This is another reason for not giving a full digitalizing dose in a single injection.

Individualize the dosage schedule for each patient.

#### Oral Administration of the Digitalis Drugs

Urgency	Drug	Dosage
Moderate	Digitalis	0.4 Gm (6 gr) q 8 hours for 3 doses
	Digitoxin	0.4 mg q 8 hours for 3 doses
	Digoxin	1.0 mg q 8 hours for 3 doses
Intermediate	Digitalis	0.2 Gm (3 gr) t.i.d. for 2 days, or 0.1 Gm (1½ gr) q.i.d. for 3 days
	Digitoxin	0.2 mg t.i.d. for 2 days
	Digoxin	0.5 mg b.i.d. for 2 days, or 0.25-0.5 mg t.i.d. for 3 days
Least	Digitalis	0.1 Gm (1½ gr) t.i.d. for 4-5 days
	Digitoxin	0.1 mg t.i.d. for 4-6 days
	Digoxin	0.25-0.5 mg b.i.d. for 4-6 days

2 Rapid oral digitalization (within 24 hours). It is usually unwise to attempt to digitalize with a single oral dose, since nausea and vomiting are common and make it

very difficult to estimate the degree of digitalization. Multiple oral doses are usually adequate for initial digitalization. Close medical observation is required before each dose is given and further doses should be withdrawn at the first sign or symptom of toxicity (see p. 231).

3. Slow digitalization - At times it is desirable to digitalize slowly over the course of a week especially if the patient cannot be closely observed during this period. Any of the digitalis preparations can be given in daily doses 2 or 3 times the average maintenance dose for 5-7 days. The total digitalizing dose may be somewhat greater than when digitalization is rapid. As soon as toxic symptoms appear the drug should be stopped for one day and the patient given the average maintenance dose.

**B Partially Treated Cases** If a digitalis preparation has been taken within 2 weeks, give one-fourth of the estimated digitalizing dose and then give additional digitalis cautiously, observing the response.

#### Maintenance Doses & Methods.

The oral route is preferred in maintaining digitalization. The exact maintenance dose must be determined clinically for each patient.

### QUINIDINE\*

Quinidine is a valuable drug in the management of most cardiac arrhythmias. It increases the effective refractory period of cardiac muscle, slows the rate of atrial and ventricular conduction, decreases the excitability of the myocardium, reduces vagal tone, and has a general depressant action on smooth muscle, causing vasodilatation. As far as conversion of atrial fibrillation is concerned several of these pharmacologic actions oppose each other, the clinical effect depends upon which action predominates.

Quinidine can be given orally, I M, or I V, as occasion demands. The I V route should be used only in urgent situations by physicians experienced in the use of the drug. Quinidine is rapidly absorbed following oral administration, reaches a peak level of effectiveness in about 2 hours, and is excreted

slowly, about 30% of the peak level remains after 12 hours. Only 10-20% of orally administered quinidine is excreted in the urine, the remainder is metabolized in the body.

After 5 or 6 doses have been given at two-hour intervals, no significant rise in blood level occurs with further doses at the same interval. When a fixed dose of quinidine is given 4 times a day, as in a maintenance schedule, the blood level rises progressively but more slowly, reaching a maximum in about 48-72 hours. The midday blood levels then remain more or less the same as long as this same schedule is maintained. If higher blood levels are desired, the individual dose must be increased or the interval between doses shortened. Because 30-40% of the peak blood level of quinidine is still present in the serum 12 hours after the last of a series of repeated doses of quinidine, a fixed dosage schedule such as 0.4 Gm. (6 gr.) every 2 hours for 5 doses can be repeated for several days to produce increasing concentrations of quinidine in the blood.

Long-acting quinidine preparations are being studied and may prove useful clinically.

#### Indications & Contraindications.

Conflicting opinions have been expressed by cardiologists on the indications, dosages, and dangers in the use of quinidine. It must be remembered that patients taking quinidine have organic cardiac disease, unpredictable accidents occur even when quinidine is not given.

**A Indications** Most clinicians agree that quinidine is a valuable drug in the management of ventricular tachycardia, atrial flutter if digitalis fails to produce sinus rhythm, and paroxysmal atrial and nodal tachycardia, and for the prevention of recurrent paroxysmal arrhythmias and the suppression of frequent premature beats, especially following myocardial infarction, after surgery, and in similar clinical situations. Quinidine is also used for conversion of atrial fibrillation to sinus rhythm, but most cardiologists feel that the presence of marked cardiac failure, serious organic heart disease, and active rheumatic fever are relative contraindications to the use of quinidine.

**B Contraindications** Quinidine idiosyncrasy is an absolute contraindication to the use of quinidine. Relative contraindications are complete heart block, bundle branch block, thyrotoxicosis, acute rheumatic fever, and subacute bacterial endocarditis.

\*Quinine may be used, but is only about 30% as effective as quinidine. Only quinidine will be discussed here.

### Preparations & Routes of Administration.

A. Quinidine sulfate should be given orally except when parenteral quinidine is specifically indicated.

B. The I. M. preparations can be used if the patient is unable to take the medication orally and the situation is not critical. Give one of the following (1) quinidine gluconate, 0.8 Gm. (12 gr.) in 10 ml. ampules, (2) quinidine sulfate, 20% solution in propylene glycol; (3) quinidine hydrochloride, 15% solution in urea and antipyrine.

C. An I. V. preparation should be used only when great urgency requires it and only by a physician familiar with the use of the drug. Quinidine gluconate, 0.8 Gm. (12 gr.) in 10 ml. ampules, can be diluted with 50-100 ml. of 5% glucose and given slowly I. V. at a rate of 1 ml./minute.

### Toxicity.

A. The myocardial toxicity is the most important and should be specifically looked for when quinidine is used. The earliest effects are seen on ECG, prolongation of the Q-T interval and QRS interval, and ventricular premature beats or ventricular tachycardia.

B. Nausea, vomiting, and diarrhea may be sufficiently severe to require cessation of the drug.

C. Cinchonism: Tinnitus, vertigo, and headache may be severe enough to necessitate withdrawal of the drug. Caution: When the QRS interval becomes more than half again as wide as before treatment, or when runs of ventricular premature beats or ventricular tachycardia occur, quinidine should be stopped immediately. In rare instances ventricular tachycardia may progress to ventricular fibrillation and sudden death.

In patients with atrial fibrillation who are converted with quinidine transient sino-atrial block may occur at the time of conversion and nodal rhythm may be temporarily noted. This has no clinical significance. Transient prolongation of the P-R interval occasionally occurs when sinus rhythm follows quinidine conversion of atrial fibrillation, this usually subsides spontaneously with smaller maintenance doses.

### D. Other Cardiovascular Effects

1. Hypotension may occur when large doses of quinidine are used or if the drug is given parenterally. It rarely is significant with ordinary oral doses.

2. Emboli occur in about 1% of patients with chronic atrial fibrillation converted with quinidine. The incidence is higher in untreated atrial fibrillation; in fact, atrial fibrillation with frequent emboli is an important reason for attempting to convert to sinus rhythm. Anticoagulants are advised for 1-2 weeks before conversion to prevent the development of new thrombi in the atria in patients with a history of recent emboli.

E. Idiosyncrasy: Fever, purpura, rash, or severe hypotension following a test dose of 0.1 Gm. (1½ gr.).

### Conversion to Sinus Rhythm.

The patient should be under constant observation, preferably in a hospital. Give a test dose of 0.1 Gm. (1½ gr.) and wait 2 hours to exclude the possibility of idiosyncrasy.

If the patient has atrial fibrillation or atrial flutter, complete digitalization is advised to slow the ventricular rate and to improve cardiac function. If digitalis is not used, the decreased strioventricular conduction resulting from quinidine may cause a rise in ventricular rate of 30-50 beats per minute and may force cessation of quinidine therapy.

For a patient with chronic arrhythmia in cardiac failure in whom immediate conversion is not essential, additional measures (e.g., sodium restriction, diuretics) are indicated before quinidine is given. The patient should be ambulatory for 2 weeks to decrease the likelihood of venous thrombosis. One week of anticoagulant therapy may be desirable, but the data are incomplete regarding its value.

Give 0.4 Gm. (6 gr.) every 2 hours for 5-6 doses on the first day, this produces an average blood level of 6-7 mg./L. Each succeeding dose produces a smaller increment in the blood level, and if conversion does not occur after 5-6 doses larger amounts must be given. In urgent circumstances, begin immediately after the fifth dose, otherwise it is best to wait until the next morning and begin again with 0.6 Gm. (9 gr.) every 2 hours. Giving the drug more frequently than every 2 hours is not warranted since it takes that long for the peak effect of the preceding dose to be reached. In most cases 0.6 Gm. (9 gr.) every 2 hours for 5 doses will convert the arrhythmia to sinus rhythm. If it does not, higher doses can be used if no toxicity has been encountered and it is urgent to convert the arrhythmia. Eighty per cent of the successful conversions occur with daily doses of 3 Gm. (45 gr.) or less.

Increasing quinidine effect can be roughly estimated by serial determinations of blood

quinidine levels by determining the rate of fibrillation and by measurement of the Q-T and QRS intervals. Rate of fibrillation is best determined on  $V_1$ , the right precordial lead in the ECG. The atrial rate is slowed markedly in atrial fibrillation as the rate approaches 200-250/minute; conversion is near. As Q-T and QRS widen up to 25-30% above the initial values, significant quinidine effects can be predicted.

## NITRITES & NITRATES

The nitrites are smooth muscle relaxants. Whether diseased coronary arteries are able to dilate in response to nitrite administration has recently been questioned. Some measurements suggest that relief of angina is due to a decrease in cardiac work subsequent to a fall in BP and cardiac output.

### Rapid Acting

The rapid-acting preparations (glyceryl trinitrate and amyl nitrite) are useful in terminating an episode of angina or in preventing it if given just before exercise.

**A Glyceryl Trinitrate Tablets (Nitro glycerin)** Place one tablet (0.3-0.6 mg  $\frac{1}{100}$ - $\frac{1}{200}$  gr) under tongue p r n. Effective in 1-2 minutes; effect lasts 15-40 minutes.

**B Amyl Nitrite Pearl** Break pearl (contains 0.2 ml) in cloth and inhale p r n. Effective in 10 seconds; effect lasts 5-10 minutes.

### Long-Acting Nitrates

The usefulness of these preparations has not been clearly established. The onset of their effect after single doses is delayed for 15-60 minutes but persists for 4-6 hours. Repeated doses may lead to tolerance, and the results of clinical trials are at best conflicting.

The following organic nitrates are administered orally or sublingually 4 times each day.

**A Pentaerythritol tetranitrate (Peritrate<sup>®</sup>)** 10-20 mg

**B Erythrol tetranitrate (Cardilate<sup>®</sup>)** 15 mg (sublingually)

**C Mannitol hexanitrate (Nitranitol<sup>®</sup>)** 15-60 mg

**D Troinitrate phosphate (Metamine<sup>®</sup> Nitretamin<sup>®</sup>)** 2-4 mg

**E Isosorbide dinitrate (Isordil<sup>®</sup>)** 10 mg

## XANTHINES

Cardiac catheterization and metabolic balance studies have demonstrated that xanthines increase the cardiac output, increase renal blood flow and glomerular filtration rate and enhance the excretion of sodium and water; they therefore may be valuable in the treatment of cardiac failure. They have also been shown to increase the coronary blood flow when used in large doses and may on occasion be helpful in angina pectoris.

### Preparations.

**A Oral** A variety of official preparations are available. A satisfactory one is aminophylline (enteric coated), 0.1-0.2 Gm (1½-3 gr) 4-6 times per day.

**B Parenteral** Aminophylline injection 0.25-0.5 Gm (¾-1½ gr) I V slowly over a five minute period or I M; may repeat in 2-4 hours.

**C Rectal suppositories** containing aminophylline 0.3-0.5 Gm (½-1½ gr) may be valuable in an impending attack of cardiac asthma or in nocturnal angina pectoris.

## DIURETICS

Diuretics are drugs which suppress renal tubular reabsorption of sodium. They are used in the treatment of diseases associated with excess sodium retention and consequent fluid accumulation (edema), e.g., congestive heart failure. The orally active diuretics have also been used in the treatment of hypertension, since sodium depletion (as well as other mechanisms) potentiates the effects of hypotensive drugs.

### Thiazide (Thiodiazine Disulfonamide) Diuretics

Drugs of this class have the great advantage of being effective in oral form. The marked sodium loss which they cause is accompanied by potassium diuresis of a potentially toxic degree, especially if digitalis is



being given concurrently. These sulfonamide derivatives have only a slight carbonic anhydrase inhibiting effect.

The thiazide diuretics are useful in potentiating the effect of hypotensive drugs and in the treatment of edema due to congestive heart failure, renal disease, cirrhosis, and other sodium retention states. They also may be used in the treatment of diabetes insipidus.

The thiazides are contraindicated in acute renal failure and must be used in smaller doses and with careful observation in cirrhotic patients and in patients receiving digitalis.

Potassium depletion is the principal toxic effect, and is most likely to occur early in the use of these drugs when diuresis is most marked. If the diet is deficient in fresh fruits and vegetables, potassium chloride (or a similar potassium salt), 1 Gm. 3-4 times daily should be given. The possibility of precipitating digitalis toxicity by potassium diuresis must be considered in patients receiving digitalis.

Other toxic effects are allergic reactions such as skin rashes, pruritus, and, rarely, bone marrow depression, gastrointestinal disturbances, photosensitization, elevated serum uric acid, with the precipitation of gout, and impaired glucose tolerance.

#### Thiazide Diuretics

	Daily Dose*
Benzthiazide (NaClex <sup>®</sup> )	25-100 mg
Benzhydroflumethiazide (Naturetin <sup>®</sup> )	5-10 mg
Chlorothiazide (Diuril <sup>®</sup> )	250-1000 mg.
Chlorthalidone (Hygroton <sup>®</sup> )	50-200 mg
Flumethiazide (Ademol <sup>®</sup> )	250-1000 mg.
Hydrochlorothiazide (Esidrix <sup>®</sup> , Hydro-Diuril <sup>®</sup> , Oretic <sup>®</sup> )	25-100 mg.
Hydroflumethiazide (Saluron <sup>®</sup> )	25-100 mg.
Methyclothiazide (Enduron <sup>®</sup> )	2.5-10 mg.
Polythiazide (Renese <sup>®</sup> )	1-4 mg
Trichlormethiazide (Naqua <sup>®</sup> , Metahydrin <sup>®</sup> )	2-8 mg

\*Give in 2 divided doses each day except for chlorthalidone, which is given daily or 3 times a week.

It is generally agreed that the amount of sodium in the diet should be kept reasonably constant. Most investigators suggest restricting sodium in order to reduce the dose of the diuretic.

The available thiazides are listed below. Outside of the laboratory there is no basis for preferring one to another. Chlorthalidone (Hygroton<sup>®</sup>) is not a thiodiazine but a sulfonamide which is otherwise similar to the other drugs listed. In treating edema a large dose may be used initially if necessary, but the dose should be decreased rapidly and doses given at longer than daily intervals if "dry" weight is maintained.

#### Mercurial Diuretics.

Intramuscularly or subcutaneously administered mercurial diuretics, which were standard drugs for many years, are slightly more potent than the thiazide diuretics. They cause less potassium diuresis, but are more often responsible for sodium depletion. No satisfactory oral preparations are available. The mercurial diuretics are now used only for an occasional difficult patient with congestive heart failure and usually only after a trial with an oral diuretic.

The dose of each of the following mercurial diuretics is 0.5-2 ml. of the prepared solution given no oftener than once daily. Chlormerodrin (Neohydrin<sup>®</sup>), meralluride (Mercurhydrin<sup>®</sup>), mercaptomerin (Thiomerin<sup>®</sup>), mercurophylline (Mercuzanthin<sup>®</sup>), mercuratiline (Cumertiline<sup>®</sup>), merethoxylline procaine (Dicurin Procaine<sup>®</sup>) and mersalyl (Salyrgan<sup>®</sup>).

#### Carbonic Anhydrase Inhibitors.

These drugs, exemplified by acetazolamide (Diamox<sup>®</sup>), are sulfonamide derivatives which depress the renal tubular reabsorption of bicarbonate. This action leads to only a transient and minor sodium diuresis but a persistent decrease of plasma bicarbonate concentrations and increase of plasma chloride concentration. Administered once or twice a week, these drugs are sometimes useful in the treatment of congestive failure associated with cor pulmonale or to potentiate the action of mercurial diuretics. They are given continuously in the treatment of glaucoma and epilepsy.

Carbonic anhydrase inhibitors may cause drowsiness, paresthesias, and minor allergic reactions.

For diuresis, acetazolamide (Diamox<sup>®</sup>) is given in doses of 250-500 mg 2-3 times per week. Ethoxzolamide (Cardrase<sup>®</sup>) is used in 62.5-125 mg. doses. Experience with dichlorophenamide (Daranide<sup>®</sup>) and methazolamide (Neptazane<sup>®</sup>) is limited to their use in glaucoma.

**Aldosterone Antagonist**

Spironolactone (Aldactone A®) is an antagonist to aldosterone the adrenal steroid which controls renal tubular reabsorption of sodium. It therefore causes sodium diuresis without potassium loss. It can be combined with a thiazide to neutralize the potassium wasting effect of the latter drug. The onset of effect may be delayed for as long as a week. The response of patients with congestive failure and primary aldosteronism has been variable. The drug should be regarded as a promising supplementary diuretic in the resistant edema of cirrhosis and nephrosis but it is expensive and has not been completely evaluated as yet. Initial dosage is 25 mg 4 times daily. Drowsiness, breast tenderness, hyponatremia, hyperkalemia and hypotension may occur.

**PROCAINAMIDE HYDROCHLORIDE**

Procainamide (Pronestyl®) depresses ectopic pacemakers, prevents arrhythmias under cyclopropane anesthesia following epinephrine and is useful in the treatment of nodal and ventricular arrhythmias. To a lesser degree it can be used to prevent these arrhythmias. It has a much less potent effect on the atria than on the ventricular arrhythmias. Whether procainamide or quinidine is the drug of choice in the ventricular arrhythmias has not been settled.

**Dosage & Administration**

**A Oral Preparation** (250 mg capsules) 0.25-1 Gm orally every 4-6 hours is the recommended dose.

**B I M Preparation** (1 Gm ampules in 10 ml diluent) The peak effect occurs within 15-60 minutes and a significant blood level is still present after 6 hours. The blood level is higher and the decrease is slower in patients with congestive failure and renal insufficiency. Hypotension is infrequent with 1 M use of the drug in the above dosage.

**C I V Preparation** (1 Gm ampules in 10 ml diluent) Can be used for ventricular tachycardia of a severe or urgent nature. The drug should be given very slowly 50-100 mg/minute up to a dose of 1 Gm, with continuous BP and if possible ECG control.

**Toxicity**

The toxicity of procainamide is the same as that of quinidine (with the exception of cinchonism).

**A Severe Hypotension** This is noted particularly with the parenteral use of procainamide and may be severe enough to require withdrawal of the drug. This is why frequent BP determinations are necessary.

**B Conduction Defects** Prolongation of the QRS interval may occur as with quinidine.

**C Ventricular arrhythmias** may occur as with quinidine.

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## Peripheral Vessels

John H Windesheim & Frank H Leeds

### EXAMINATIONS & TESTS OF PERIPHERAL ARTERIAL FUNCTION

#### TESTS OF PERIPHERAL ARTERIAL INSUFFICIENCY

There are many tests of peripheral arterial insufficiency which are useful in research but are not necessary or not feasible in office practice. The tests outlined below are those which may be performed under the usual conditions of medical practice and which are of most value in the evaluation and management of arterial insufficiency.

#### Postural Tests.

The simplest test of peripheral arterial insufficiency is to note changes in the color of the skin and filling of superficial veins with elevation and dependency of the limbs. When a normal person's hand or foot is raised 65 cm (26 inches) or more above heart level it may become slightly paler. When there is impairment of the blood flow to a foot or hand the extremity becomes markedly pale when elevated. This is because elevation empties the vascular bed through the venous system and blood enters the small vessels from the arterial side too slowly to keep them sufficiently distended. In borderline cases pallor of the foot may not occur with simple elevation but may be elicited when the patient flexes and extends his foot at the ankle.

After elevation the limb is placed in a dependent position. With normal circulation the color usually returns in 10-15 seconds. With severe impairment of circulation the delay in return of color may be 60 seconds or more. Thereafter the affected extremity may develop abnormal rubor. In isolated or superimposed occlusion of small arteries of the hand or foot the color may return in a patchy distribution.

When the circulation is impaired elevation will also cause collapse of the superficial

veins of the dorsum of the foot or hand. If after the limb is placed in the dependent position it takes more than 10-15 seconds for the veins to fill the blood flow to that limb is abnormally slow. The delay in filling of the superficial veins is roughly related to the degree of impairment of arterial circulation.

#### Reactive Hyperemia Tests.

**A Allen's Test.** Reactive hyperemia is the increase in the flow of blood upon withdrawal of temporary circulatory occlusion. This test may be useful in the upper extremity to demonstrate patency or occlusion of the ulnar artery when the ulnar pulse cannot be palpated (Allen's test). It is performed in the following manner: The hand is raised the fist closed the wrist grasped tightly by the observer. The hand is opened and closed until pallor occurs. The hand is then lowered and the fist opened. After 1-2 minutes the wrist is released but the pressure is maintained on the radial pulse. If the ulnar artery is patent there will be an immediate flush over the entire hand. If the ulnar artery is occluded the hand may remain completely or partially blanched until the radial artery is released. Occlusion of one of the paired digital arteries may be demonstrated in a similar manner.

**B Reactive Hyperemia With Elevation.** The reactive hyperemia test with elevation is a simple reliable method of evaluating peripheral arterial insufficiency of the upper or lower extremity and its response to treatment. It may be useful in evaluating treatment and in determining the prognosis of ischemic ulcers of the foot.

**1. Technic.** - (1) The patient is placed supine and the brachial BP taken. (2) The toes are raised to 65 cm (26 inches) above the atrial level and observed for blanching. (The atrial level is taken as 7 cm (2 3/4 inches) below the junction of the manubrium and the body of the sternum (angle of Louis)). (3) If no blanching occurs the feet remain elevated and BP cuffs are inflated just above the ankle to a pressure 50 mm Hg above brachial systolic

pressure The occlusive cuffs are left on for 5 minutes (4) At the end of that time, with the feet still elevated, the pressure in the cuffs is suddenly released and the feet observed for return of color (5) If at the end of one minute color has not returned, the feet are lowered 5 cm (2 inches) and then lowered 5 cm every 30 seconds until color returns The level at which color returns is noted

2 Interpretation - (1) If the filling pressure (level at which color returns) is 40 cm (16 inches) or more above the atrium, spontaneous healing of an ulcer will occur or, if amputation is necessary through the foot, the amputation site will heal (2) If the filling pressure is less than 40 cm (16 inches), a more extensive procedure (e.g., sympathectomy, thromboendarterectomy, or drug therapy) must be done to help raise the pressure

### Oscillometry.

An oscillometer is a device for magnifying and measuring volume changes during diastole and systole in peripheral arteries under varying pressures It consists of a cuff and a recording instrument Crude measurements can be made with a sphygmomanometer

Oscillometry is most helpful to the surgeon in ascertaining the exact level of arterial occlusion or in helping to establish the presence or absence of pulses which are not palpable because of overlaid muscle, fat or edematous tissue Great fluctuations in blood flow such as are induced by cold and heat in the skin and by rest and exercise in muscles change the oscillometric readings It is therefore best to examine the patient after he has been allowed to rest comfortably in a warm room and to compare readings at identical levels in the 2 extremities Slight discrepancies in adjustment of the cuff may be a source of error

### Claudication Tests.

Tests of intermittent claudication are the most practical means of estimating blood flow through muscle An adequate estimate can usually be obtained from the patient's statement concerning the walking distance necessary to precipitate pain A more accurate method is by having the patient walk at some standard rate, such as 120 steps/minute, and carefully noting the distance at which claudication occurs

Another method is to reproduce the symptoms by asking the patient to walk over standard steps at a standard rate

These tests are useful in assessing the severity of the symptoms and also in observing improvement after treatment or worsening of the disease. They are useful also when the pa-

tient is unable to give a satisfactory history of intermittent claudication and in differentiating between intermittent claudication, faulty mechanism of an orthopedic nature, neurologic disorders, and neuroses

## X-RAY EXAMINATION OF THE ARTERIES

The arteries cannot usually be seen on x-ray unless the walls are calcified, but there is no relationship between calcification and patency of an artery In some cases an arterial aneurysm may be outlined by the calcification of its wall In order to determine the exact site and extent of an arterial occlusion, the exact nature of an arterial aneurysm, or the site and character of abnormal communications between arteries and veins, a radioopaque material is injected into the artery and x-rays taken at appropriate intervals to outline the arterial tree The usual injection sites are the aorta above or below the renal arteries, the brachial artery just above the bifurcation, and the common femoral artery at the groin The safest and least irritating contrast materials are 50% diatrizoate (Hypaque®) and 76% methylglucamine-diatrizoate (Renografin®). These substances produce minimal arterial spasm and are well tolerated by the kidneys

Arteriograms are not necessary in most cases but give invaluable information when planning a direct surgical attack on an arterial lesion They may be useful also in differentiating between arteriosclerosis obliterans and thromboangiitis obliterans.

Arteriograms are not difficult to interpret Normal vessels have a smooth, uninterrupted configuration and take a fairly direct course, and there is a minimum of collateral circulation In occlusive arterial disease the contour of the artery is irregular, the artery may be completely absent over a large area of occlusion, and there are numerous tortuous collateral arteries

## DISEASES OF THE PERIPHERAL ARTERIES

### ARTERIOSCLEROSIS (ATHEROSCLEROSIS) OBLITERANS (ASO)

#### Essentials of Diagnosis

- Discomfort in the legs thighs or buttocks occurring during exercise and relieved by immobility
- Impaired arterial pulsations systolic bruit over large arteries
- Patchy calcification of vessels on x-ray
- Older age group especially men often with diabetes mellitus, hypertension and elevated blood lipids

Distinguish from other arterial obliterative diseases such as thromboangiitis obliterans and scleroderma. The changes in skin color and the ulcerations must be differentiated from those of Raynaud's disease and chronic venous insufficiency, extremity pains from the pain of nonvascular diseases such as arthritis and spinal cord lesions. If the clinical manifestations are those of acute arterial occlusion arterial embolism and simple arterial thrombosis must be considered.

#### General Considerations

Arteriosclerosis obliterans is primarily a disease of older men although about 15-20%

occur in women. The incidence seems to be increasing in the 30-50 age group. Many cases first diagnosed as thromboangiitis obliterans are now considered to be variants of arteriosclerosis obliterans.

Diseases which predispose to arteriosclerosis obliterans include the hyperlipemic states (e.g. myxedema, familial xanthomatosis, xanthoma tuberosum) and the nephrotic syndrome, diabetes mellitus and hypertension. Other disorders which may hasten thrombosis on atherosclerotic plaques are certain blood dyscrasias (especially polycythemia vera), heart failure, severe injury, infectious diseases and major surgical procedures.

#### Clinical Findings

**A. Symptoms and Signs.** Symptoms may be gradual in onset or may appear rapidly over a period of hours as a result of sudden arterial occlusion. Intermittent claudication, the most common symptom, may be defined as a discomfort in any part of an extremity which occurs only during exercise and is relieved quickly by rest without change in position of the limbs. The discomfort is most commonly in the calf but may occur in the foot, thigh, hip region or buttocks. With occlusion of a subclavian or axillary artery, arm or hand claudication may be present. With severe degrees of ischemia, prethoracic (rest) pain may be present, primarily in the foot and occurring mostly at night, forcing the patient to sit up for hours in order to get relief. The pain of ischemic neuropathy (extending over large areas of an extremity) may also be present.

Differential Diagnosis of Common Peripheral Vascular Diseases

	Raynaud's Disease	Thromboangiitis Obliterans (TAO)	Arteriosclerosis Obliterans
Sex	70-80% females	99% males	Over 75% males
Age at onset	10-50 years	20-35 years	Over 40 years
Extremities involved	Usually upper but may occur in lower	40% upper over 88% in lower	Always lower rarely upper
Symmetry	Symmetric and bilateral	Asymmetric and usually bilateral	Asymmetric and usually bilateral
Peripheral arterial pulsations	Present	Absent or diminished	Absent or diminished
Usual sites of gangrene	Small areas at tips of fingers and toes	Variable	Variable
Venous involvement (phlebitis)	Absent	Often present	Absent
Calcification in arteries	Absent	Rare	Usually present
Diabetes mellitus	Usually absent	Usually absent	Present in 20% of cases
Plasma lipids	Normal	Normal	Frequently elevated

Various types of sensory disturbances and actual muscular weakness may occur with severe degrees of ischemia.

Impairment of arterial pulsations either unilaterally or bilaterally and most often in the lower extremities is the most consistent finding. Systolic bruits over large arteries whether pulsating normally or of diminished quality are an extremely valuable sign in evaluating a patient with symptoms of arterial occlusion. In more severe cases of arteriosclerosis obliterans, elevation, pallor and dependent rubor of the feet and toes will be present and a lower skin temperature of the involved extremity can usually be detected by simple palpation. Ulceration or gangrene occurring most often as a result of trauma may affect the toes, portions of the foot or an entire leg as high as the knee. Trophic skin changes manifested by thinning of the skin, nail changes and loss of hair as well as atrophy of muscles and soft tissues are other signs of advanced disease.

**B Laboratory Findings** The plasma lipid concentrations are often elevated (in about 20% of patients). An elevated packed cell volume may indicate polycythemia vera.

**C X ray Findings** Spotty calcification of the aorta or of the iliac or femoral arteries on x ray may be a helpful finding. Arteriography (primarily aortography) should not be done routinely but is essential to localize the atherosclerotic occlusive lesions prior to surgery.

### Differential Diagnosis

Thromboangiitis obliterans (TAO) occurs essentially only in men (99%) under the age of 40 and is not associated with diabetes mellitus or hyperlipemia. There is no calcification of the arteries on x ray. Involvement of small vessels in the upper extremities and superficial phlebitis occur in 40% of cases.

Absence of pulsations in small arteries (e.g. ulnar or posterior tibial) is quite common in scleroderma but only when definite skin changes are present.

Raynaud's disease is not associated with evidence of arterial occlusion. It occurs primarily in young women and causes classic color changes usually symmetrically and bilaterally, most often in the upper extremities.

Thrombophlebitis is rarely confused with arteriosclerosis obliterans although in an occasional case vasospasm during the acute phase may temporarily obliterate arterial pulsations. The swollen, hot, tender extremity of phlebitis contrasts clearly with the cold,

pulseless extremity of arteriosclerosis obliterans.

The ulceration of chronic venous insufficiency is usually in the region of the medial malleolus, an unusual site for atherosclerotic ulceration, and the ulcer of the former is usually not painful.

Nonvascular diseases (e.g. arthritis of the hip, gout) can usually be easily distinguished from arteriosclerosis obliterans since the pain described is not that of claudication (as defined above) and since the arterial pulsations are not absent or diminished in quality.

### Treatment

Treatment is primarily conservative but thromboendarterectomy, vascular grafts and sympathectomy are of great value in properly selected cases.

**A General Measures** Correct any disorder (e.g. congestive failure) which may interfere with the blood supply. Diabetes mellitus if present must be vigorously controlled. Tobacco in any form should probably be prohibited. Alcoholic beverages in moderation are not contraindicated. The diet should be low in saturated fats.

**B Local Measures** The patient should avoid extremes of heat and cold (e.g. contrast baths). Fungal infections of the feet must be controlled. Fungicidal dye solutions (e.g. Castellani's) or other antifungal agents may be used. Do not use Whitfield's ointment.

Infections of and trauma to the affected extremity must be guarded against. The patient should be given the following instructions:

1. Soak feet for 10-15 minutes in warm water (not hot water) before cutting nails.
2. Bunions or corns must be trimmed by a physician or a chiropodist.
3. Skin must be kept soft and pliant by rubbing with lanolin or a bland vegetable oil 1-2 times daily.
4. Socks should be changed at least once a day. For warmth use soft woolen socks or 2 pairs of another kind.
5. Shoes must be well fitted and have no pressure points.

**C Special Measures** The following may be used in an attempt to increase collateral circulation:

1. The most effective way to develop collateral circulation is by walking. The patient should be instructed to walk slowly up to the point of claudication at least 8 times a day. At the first symptom of beginning claudication (numbness, fatigue, aching) he should stop for 3-4 minutes.

2 Buerger's exercises - Do not use these exercises if an infection or open wound is present. Individualize the exercises for each patient. Demonstration and rehearsal are of great importance. The technic is as follows:

(1) Elevate the legs about 45° (support them on an overturned chair or against the wall) until blanching or pain occurs (usually in 1-2 minutes or less).

(2) Allow the legs to dangle freely for 2-5 minutes until maximal rubor occurs. At the same time the feet are moved downward and upward and then inward and outward. The toes are spread and closed while these movements are being made. Do each series of foot exercises 10 times. If the feet are too painful it may be necessary to eliminate these exercises.

(3) Place legs and body in a horizontal position for 2 minutes.

(4) Repeat 5 times at each session for 3-5 sessions daily.

3. Mechanical devices may be used, but it is probable that the only effective device is the oscillating bed.

4. Vasodilator drugs are usually of little or no value and, unless there is abnormal vasoconstriction, may actually be harmful. Blood flow studies show a decrease in the blood supply to the ischemic limbs of the elderly arteriosclerotic at the height of systemic vasodilation due to drugs.

#### D. Treatment of the Severe Stages of Peripheral Arterial Decompensation

1. Treatment of claudication - Teach the patient to walk slowly, take short steps, and to stop to rest before the pain of claudication is fully developed. Correct or relieve any ligamentous or arthritic disabilities by means of stretching exercises and salicylates.

2. Treat rest pain by having the patient sleep with the head of his bed elevated 20-25 cm. (8-10 inches) and by rigid limitation of activities. If edema has developed, an oscillating bed or Buerger's exercises may be prescribed.

3. Treatment of severe infection or incipient gangrene - Start antibiotics (if possible, chosen on the basis of culture or sensitivity tests) as soon as infection occurs. Keep the extremity horizontal or lowered, never elevated, the oscillating bed may be useful. Keep the foot free of dressings. Room temperature must be comfortable. Support bed clothes by use of a cradle over the affected limb or by a pillow under the bedclothes at the foot of the bed.

Drain purulent pockets thoroughly but gently. This may be accomplished by cover-

ing the crusted lesion with a few layers of petrolatum or Xeroform® gauze for 24 hours, then applying saline sponges at room temperature and changing frequently during the next 48 hours. Then dress the lesion with a bacitracin or bacitracin-neomycin ointment and a single layer of Xeroform® gauze for 2-3 days. Reinstitution this treatment when necessary.

#### E. Surgical Measures

1. Thrombo-endarterectomy or grafting procedures are especially useful in the segmental or localized occlusion of major arteries.

2. Sympathectomy is indicated if there is some evidence of abnormally increased vasomotor tone.

3. Conservative amputation (toe or transmetatarsal) is required when reactive hyperemia and elevation tests show a filling pressure in the small blood vessels of not less than 40 cm (16 inches).

4. Classical supracondylar amputation is required if the filling pressure in small blood vessels is shown by the reactive hyperemia test to be less than 40 cm (16 inches) and thrombo-endarterectomy or sympathectomy is not indicated.

#### Prognosis

Although arteriosclerosis obliterans is a chronic, progressive disease, the prognosis for survival of the affected extremity depends upon multiple factors. These include the rapidity and extent of the occlusive process, the extent of collateral circulation, the avoidance of thermal or mechanical trauma, and the frequency of recurrence of arterial occlusion. When gangrene of even minor degree is present, the prognosis for saving the limb is not favorable.

The life expectancy of patients with arteriosclerosis obliterans is definitely shortened. The major causes of death are cerebrovascular accidents and myocardial infarction.

Thrombo-endarterectomy or grafting procedures produce good results in patients with aorto-iliac occlusion, but re-thrombosis has occurred in a large number of cases of femoral artery occlusion following surgery. This has led most surgeons to abandon direct arterial surgery in cases of chronic femoral artery occlusion.

Beckwith, R., & others: Chronic aortoiliac thrombosis, a review of 65 cases. *New England J Med.* 258:721-6, 1958.

Edwards, E. A.: *Choice of therapy for peripheral arteriosclerosis.* *New England J Med.* 256:875-80, 1957.

Juergens, J. L., Barker, N. W., & E. A. Hines, Jr.: *Arteriosclerosis obliterans: review of*

520 cases with special reference to pathogenic and prognostic factors. *Circulation* 21 183-95, 1960

## ACUTE ARTERIAL OCCLUSION

### Essentials of Diagnosis.

- Numbness tingling weakness, and coldness of an extremity.
- Collapsed superficial veins, pallor of an extremity, weakness and decreased reflexes of involved area
- Absent pulsations of arteries previously known to be patent
- Onset is sudden in 50%, pain is the presenting complaint in only 50%

Distinguish from acute thrombophlebitis with arterial spasm, in which the skin temperature is normal or elevated, veins are distended, and edema is present

### General Considerations.

Acute arterial occlusion may be due to arterial embolism or to sudden arterial thrombosis. Emboli originate in 2 main sources the heart and the peripheral arteries. The more important of these is the heart, where emboli arise either from a thrombus developing in a fibrillating atrium or in a ventricle following myocardial infarction. A thrombus from a peripheral artery may also dislodge and give rise to emboli distally. This may occur in aneurysms, on atherosclerotic plaques, or in inflammatory disorders such as thromboangiitis obliterans.

Sudden arterial thrombosis in situ occurs most commonly in arteriosclerosis obliterans and thromboangiitis obliterans, and occasionally in polycythemia vera, cervical rib syndrome, heart failure, and various debilitating and infectious diseases.

### Clinical Findings.

Although sudden onset of pain in an extremity is the outstanding symptom, the presenting complaints may be numbness, tingling, coldness, or weakness of an extremity. Symptoms may develop gradually over a period of several hours.

In the area supplied by the occluded vessel the skin temperature is often lowered, pallor is often present, and, if the process continues in spite of therapy, cyanosis and gangrene may result. The superficial veins are collapsed, and there may be muscular weakness, loss of

sensation, and diminished or absent reflexes. Absence of pulsations in arteries in which pulsations were previously present is the most important diagnostic sign, and, in conjunction with pallor and decreased skin temperature of unusual degrees, is pathognomonic of arterial occlusion.

### Treatment.

**A Emergency Measures.** The following measures are used at once to prevent extension of the thrombus and reflex vasospasm. Continue postoperatively.

1. Vasodilators - Give papaverine, 60 mg (1 gr.) I.V. every 2-3 hours or, preferably, 30 mg (1/2 gr.) intra-arterially proximal to the site of occlusion. Totazoline (Priscoline<sup>®</sup>) 50 mg, may be used instead. Whisky may be given orally, 1 1/2 oz. at least 4 times daily.

2. Morphine sulfate, 10-15 mg. (1/6-1/4 gr.) I.V. stat. and repeat subcut. as needed.

3. Procaïne block of the sympathetics to the affected extremity may be helpful. Repeat as necessary, but do not use if anticoagulant therapy has been started.

4. Anticoagulant therapy should be instituted at once to prevent thrombotic extension of the embolus. Give heparin sodium, 50 mg (3/4 gr.) I.V. stat. If surgery is necessary, the heparin effect can be neutralized with protamine sulfate or hexadimethrine (Polybrene<sup>®</sup>).

5. Place the patient in an oscillating bed if one is available. Otherwise keep the extremity horizontal or slightly lower than the rest of the body.

6. A warm environment is mandatory.

**B Local Measures:** Keep the extremity horizontal or slightly lower than the rest of the body (if an oscillating bed is not available). Protect it against pressure and other trauma, and against heat or cold.

**C Surgical Measures.** Embolectomy or thrombo-endarterectomy is indicated within 10-12 hours if medical treatment is not curative.

### Prognosis.

The course depends greatly on the amount of arterial spasm which occurs in collateral vessels when a peripheral artery is suddenly occluded. If these vessels can be dilated by medical treatment, the function of the limb may be restored. If spasm persists, thromboses of the involved vessels may follow and lead to loss of the limb. The prognosis also depends on such factors as the age and general condition of the patient and on the interval between occlusion and treatment. Modern ther-



apy has markedly improved the prognosis of this serious condition.

Wessler, S., & others. Studies in peripheral arterial occlusive disease. III. Acute arterial occlusion. *Circulation* 17:512-25, 1958.

### THROMBOANGITIS OBLITERANS (TAO, Buerger's Disease)\*

#### Essentials of Diagnosis.

- Intermittent claudication, primarily in the palm of the hand or the arch of the foot.
- Trophic, ischemic skin changes of the involved digit or extremity
- Absent or impaired pulsation of an associated artery, superficial phlebitis
- Patients almost always young to middle-aged men with a history of tobacco smoking.

Differentiate from other causes of arterial occlusion such as arteriosclerosis obliterans and scleroderma, from vasospastic conditions such as Raynaud's phenomenon, livedo reticularis, and acrocyanosis, from gangrenous lesions following frostbite, from the trophic ulcerations associated with sensory loss in tabes dorsalis and syringomyelia, and from neuromuscular disorders causing painful extremities.

#### General Considerations.

Thromboangitis obliterans is a segmental inflammatory disease which obliterates small arteries and veins. The specific etiology is not known. Infection, toxic processes (e.g., ergotism), and especially tobacco smoking have been considered as possible causes. Its onset is typically in men below age 40. TAO is an uncommon condition which has often been erroneously diagnosed in cases of arteriosclerosis obliterans.

\*There is some question about the nature of this symptom complex and its exact relationship to other peripheral vascular diseases. It may be a variant of ASO. Since its clinical manifestations appear different from the classical variety of ASO, a separate discussion at this time appears warranted.

#### Clinical Findings.

Intermittent claudication (as defined in the section on arteriosclerosis obliterans) is noted in almost all cases; it occurs primarily in the arch of the foot or the palm of the hand. Pre-trophic rest pain, the pain of ischemic neuropathy, and various sensory disturbances may be present in advanced cases. Raynaud's phenomenon occasionally occurs in asymmetric distribution. Persistent coldness and pallor of an involved digit may also be present. The patient may complain of mild aching pain in an area of superficial phlebitis.

Absence or impairment of pulsations in the dorsalis pedis, posterior tibial, ulnar, or radial artery is the outstanding finding. Allen's test is of value when obstruction of the ulnar or radial artery distal to the wrist is suspected. Postural color changes will be noted in more advanced cases, and decreased skin temperature of the involved extremities or digits may be elicited by palpation. Raynaud's phenomenon, usually asymmetric in distribution, occurs in 20-30% of cases. Ulceration and gangrene of the digits, frequently around the nail margins, are often present. Trophic skin changes are indicative of severe ischemia.

Superficial phlebitis, primarily of small veins, occurs in 40% of cases. This lesion presents acutely as small, red, tender cords up to a few cm long. The most common sites are on the foot and in the ankle region, but phlebitis may be present anywhere on the upper and lower extremities.

X-rays of the involved extremity, arteriography, and skin temperature studies may be of some value but are rarely necessary in making a definitive diagnosis.

#### Differential Diagnosis

Arteriosclerosis obliterans occurs in an older age group, usually with associated hyperlipemia and vessel calcification and without associated phlebitis.

Scleroderma causes characteristic skin changes prior to definite vascular findings.

Raynaud's disease causes symmetric bilateral color changes, primarily in young women, and no impairment of arterial pulsations.

Livedo reticularis and acrocyanosis are vasospastic diseases which do not affect peripheral pulsations.

Frostbite may produce superficial gangrene. Pulsations proximal to the region of gangrene are not impaired, and there is a history of exposure to cold. Nonvascular trophic ulcers may occur in tabes dorsalis, syringomyelia, and other diseases associated with sensory loss. In these disorders pulsa-

tions are present and there are no postural color changes

Among the neuromuscular conditions, the lesions most commonly confused with thromboangiitis obliterans are protruded intervertebral disks, metatarsalgia, and other mechanical foot derangements. None of these cause typical claudication or changes in peripheral pulsations.

#### Complications.

Occlusive arterial lesions of various visceral organs have been described but few have been verified and most have actually been shown to be arteriosclerotic lesions.

#### Treatment.

Although the treatment of Buerger's disease is along the same lines as for arteriosclerosis obliterans, treatment can be more conservative since Buerger's disease has a more favorable long-term prognosis.

The most important aspect of care is strict prohibition of smoking. If the patient refuses to accept this restriction the disease is almost certain to progress in spite of any treatment.

Sympathectomy is indicated to help relieve the vasospastic manifestations to aid in establishing collateral circulation, to relieve intermittent claudication and rest pain, and to favor the development of collateral circulation to promote healing at an amputation site.

Arterial grafts may be considered when arteriograms show localized blockage of a vessel with the distal vessels open.

If the disease is well managed, amputation is usually not required. However, the indications for amputation are similar to those given for arteriosclerosis obliterans (reactive hyperemia tests). In Buerger's disease, however, a more conservative approach is used as regards conservation of tissue. If there is evidence of both large and small vessel disease or severe pain, the conservative approach may have to be abandoned and amputation resorted to.

#### Prognosis

The course depends upon the extent and rapidity of development of arterial occlusive lesions and the development of collateral channels. The disease usually becomes quiescent after many exacerbations and remissions. The prognosis for an involved limb is excellent provided early treatment (primarily cessation of the use of tobacco) is instituted.

of thromboangiitis obliterans the case against Buerger's disease. *New England J. Med.* 262:1149-60, 1960

### TEMPORAL ARTERITIS

Temporal arteritis is almost without exception a disease of men and women over 55 years of age. The etiology is not known.

#### Clinical Findings.

**A Symptoms and Signs.** For weeks or months before localizing symptoms appear there may be low-grade fever, anorexia, malaise, fatigue, and weight loss. The patient then complains of severe throbbing frontal or occipital headaches which persist for some time. The most serious manifestation is sudden or gradual loss of vision in one or both eyes (50% of cases) as a result of involvement of the central retinal artery.

The involved temporal or occipital arteries are firm, tender cords which may be nodular and are usually pulseless. Erythema in the same region is usually present. Various abnormalities may be noted on examination of the ocular fundi.

**B Laboratory Findings.** Mild anemia, leukocytosis with a shift to the left, and a markedly elevated sedimentation rate are usually present.

#### Treatment.

**A Relief of Pain.** Opiates are contraindicated because of the danger of addiction in chronic cases. In the past, excision of the involved segment of the artery was done to relieve pain. Local injections of procaine or lidocaine (Xylocaine®) are a useful means of relieving pain.

**B Steroid Therapy.** Begin steroid therapy as soon as the diagnosis is made. Ocular complications can be prevented only with these drugs, and other symptoms are also well controlled. Start with large doses (300 mg of cortisone or comparable amounts of the newer analogues). Keep dosage at 200 mg of cortisone (or equivalent) until symptoms are controlled (usually 2-5 weeks). Then reduce dosage gradually, but continue doses of 25-75 mg. of cortisone (or equivalent) until the disease has run its natural course.

#### Prognosis

Temporal arteritis is a self-limited, generally benign disease which runs its course

Horwitz, O. Buerger's disease retrieved. *Ann Int Med* 55:341-4, 1951  
Wessler, S., & others. A critical evaluation

in 2 months to 2 years. Visual impairment is usually permanent and is the most serious complication

## ACROCYNANOSIS

Acrocyanosis is an uncommon vasospastic disturbance of the small arterioles of the skin of unknown etiology. It may occur at any age and is most common in women. The patient usually complains of persistent, long-standing coldness, sweating, and bluish discoloration of the fingers, hands, toes, and feet. There may be some swelling, but no pain. The symptoms are usually worse during cold months. There are no helpful laboratory findings.

Treatment consists of reassuring the patient that this is an entirely benign condition, protection from cold, and, rarely (in severe cases), sympathectomy.

The color changes may persist for life.

Estes, J E Vasoconstrictive and vasodilative syndromes of the extremities. *Mod Concepts Cardiovas Dis* 25:355-60, 1956

## RAYNAUD'S DISEASE

### Essentials of Diagnosis

- Paroxysmal bilateral symmetric pallor and cyanosis followed by rubor of skin of extremities
- Precipitated by cold or emotional upset, relieved by warmth
- Absence of or only minimal gangrene
- Primarily a disorder of young women

Differentiate from the numerous disorders which may be associated with Raynaud's phenomenon, including occlusive arterial diseases, neurogenic lesions, scleroderma, disseminated lupus erythematosus, and the cryoglobulinemias, and from other vasospastic diseases, primarily acrocyanosis and livedo reticularis.

### General Considerations

Raynaud's disease is the primary or idiopathic form of paroxysmal digital cyanosis. Raynaud's phenomenon is the secondary form of paroxysmal digital cyanosis.

In Raynaud's disease the digital arteries respond excessively to vasospastic stimuli.

The etiology is not known, but some abnormality of the sympathetic nervous system seems to be active in this entity. The disease occurs primarily in females between puberty and age 40, and a family history of a vasospastic phenomenon can often be obtained.

### Clinical Findings

The classical description of Raynaud's disease is that on exposure to cold or in response to an emotional stimulus, the tips of the fingers of both hands become first pale and then cyanotic, often with numbness, coldness, and perspiration. With prolonged cyanosis, there may be aching and awkwardness of motion. The attack usually terminates spontaneously or upon remaining in a warm room or upon placing the part in warm water. During recovery there is intense rubor, throbbing, paresthesia, and slight swelling. Initially only one hand may be involved, but eventually the disorder becomes bilateral and symmetric.

As the disorder progresses, the color changes may involve more proximal parts of the fingers, the hands and feet. Small trophic lesions and small gangrenous ulcers may appear on the fingertips. Severe pain, acrosclerodactylia and contractures eventually may cause considerable disability. Extensive gangrene never occurs.

Raynaud's phenomenon differs from Raynaud's disease only in that it is more often unilateral or involves only 1-2 fingers.

Between attacks there may be no abnormal findings. For diagnostic purposes an attack should be induced if possible by exposure of the hands or the whole body to cold. Peripheral pulses are normal.

### Differential Diagnosis

Differentiation must be made between Raynaud's disease and the numerous disorders which may be associated with Raynaud's phenomenon. These include thromboangiitis obliterans, arteriosclerosis obliterans, cervical rib, scalenus anticus syndrome, collagen diseases, and disorders characterized by cold agglutinins and cryoglobulinemia.

The differentiation from TAO is usually not difficult. TAO is a disease of men, and when Raynaud's phenomenon occurs in TAO it usually occurs in one or 2 digits only. The absence of weakness of peripheral pulses rules out the possibility of Raynaud's disease and is essential also in differentiating Raynaud's disease from ASO. ASO occurs generally in an older age group, and Raynaud's phenomenon in this condition is rarely bilateral or symmetric.

Raynaud's phenomenon commonly occurs in patients with cervical ribs or the scalenus anticus syndrome. The symptoms in these disorders are generally unilateral and brachial plexus compression symptoms tend to dominate the clinical picture. The various maneuvers and tests helpful in diagnosing these conditions should be performed on any patient with unilateral Raynaud's phenomenon.

It may be difficult to differentiate the skin thickening in Raynaud's disease from the early stages of scleroderma with Raynaud's phenomenon. If Raynaud's phenomenon has been present for some years but sclerodermatous changes are minimal, the diagnosis of Raynaud's disease is more likely. The skin of the face, neck, and chest are involved in the later stages of scleroderma, and esophageal involvement is manifested by dysphagia.

Raynaud's phenomenon is occasionally the presenting complaint in systemic lupus erythematosus.

Cryoglobulins are abnormal proteins which are precipitated on exposure to cold and cause a disorder simulating Raynaud's disease. They are usually found in serious diseases and the diagnosis is not difficult. Testing for cryoglobulins may be worthwhile in atypical cases of Raynaud's phenomenon.

In acrocyanosis, the cyanosis of the hands is permanent and diffuse.

### Treatment

Most mild cases of Raynaud's disease are successfully treated by the avoidance of cold and injury to the fingers. In more severe cases, dilatation of the cutaneous vessels to the skin of the hands by means of dorsal sympathectomy is probably still the most effective method of treatment. Because sympathetic activity tends to return in 2-5 years, sympathectomy should be reserved for severe cases. These patients should stop smoking.

The use of vasodilator drugs such as tolazoline (Priscoline<sup>®</sup>) 25-50 mg 3-4 times daily or nylidrin (Arlidin<sup>®</sup>) 6 mg 3-4 times daily after meals may be of value. Lithyronine (Cytomel<sup>®</sup>) 25 mcg q.i.d. and reserpine 0.25-0.5 mg daily have been effective in some cases (Peacock).

### Prognosis

Raynaud's disease is usually benign, causing mild discomfort on exposure to cold and progressing very slightly over the years. In a few cases, rapid progression does occur, so that the slightest change in temperature may precipitate the color changes. It is in this situation that sclerodactylia and small areas of gangrene may be noted, and these patients

may become quite disabled by severe pain and limitation of motion and secondary fixation of distal joints.

Estes J E See reference under Acrocyanosis p 247

Gifford R W Jr The clinical significance of Raynaud's phenomenon and Raynaud's disease. *M Clin North America* 42:963-70, 1958

Gifford R W Jr Hines E A Jr & W McK Craig Sympathectomy for Raynaud's phenomenon. *Circulation* 17:513, 1958

## LIVEDO RETICULARIS

Livedo reticularis is a vasospastic disorder of unknown etiology which causes a constant mottled discoloration on large areas of the extremities. It occurs primarily in young women.

Patients with this disorder complain of a persistent bluish mottling of the lower extremities at times involving only the lower portions but occasionally involving the thighs and the hands and arms (usually to a lesser degree). The color may change to a reddish hue in warm weather but never entirely disappears spontaneously. A few patients complain of paresthesias, coldness, or numbness in the involved areas. Rarely, a history of recurrent ulcerations in the lower extremities can be obtained.

Bluish mottling of the extremities is diagnostic. The peripheral pulses are normal. The extremity may be cold with increased perspiration.

Livedo reticularis must be differentiated from acrocyanosis, Raynaud's disease, and organic occlusive diseases.

Treatment consists of protection from exposure to cold and vasodilators (e.g. tolazoline 25-50 mg q.i.d.) in more severe cases. If ulceration or gangrene is present, bed rest, compresses, vasodilators, and occasionally sympathectomy may be indicated.

In most instances, livedo reticularis is entirely benign. In a few patients, recurrent ulceration and even gangrene may require periodic hospitalization.

Barker N W Hines E A & W McK Craig Livedo reticularis. A peripheral arterial disease. *Am Heart J* 21:592-604, 1941

## ERYTHROMELALGIA (Erythromelalgia)

Erythromelalgia is a paroxysmal bilateral vasodilative disorder of unknown etiology. Idiopathic (primary) erythromelalgia occurs in otherwise healthy persons, rarely in children, and affects men and women equally. A secondary type is occasionally seen in patients with polycythemia vera, hypertension, gout, and organic neurologic diseases.

The chief symptom is bilateral burning distress lasting minutes to hours, first involving circumscribed areas on the soles or palms (or both) and then, as the disease progresses, the entire extremity. The attack occurs in response to stimuli producing vasodilatation (e.g., exercise, warm environment), especially at night when the extremities are warmed under the bedclothes. Relief may be obtained by cooling the affected part and by elevation. Reddening or cyanosis as well as heat may be noted.

No findings are generally present between attacks. On induction of the syndrome, heat and redness will be noted in association with the typical pain. Skin temperature and arterial pulsations are increased, and the involved areas may sweat profusely.

Erythromelalgia must be differentiated from peripheral neuritis and organic occlusive diseases, and from acrocyanosis.

In primary erythromelalgia, aspirin may give excellent relief. The patient should avoid warm environments. In severe cases, if medical measures fail, section or crushing of peripheral nerves may be necessary to relieve pain.

Primary idiopathic erythromelalgia is uniformly benign. The prognosis in secondary erythromelalgia depends upon the underlying disease.

Estes, J. E.\* See reference under Acrocyanosis, p. 247.

## REFLEX SYMPATHETIC DYSTROPHY (Causalgia)

### Essentials of Diagnosis

- Burning pain and hyperesthesia in an extremity associated with cyanosis and coldness
- Atrophy of skin and muscle may be present
- History of preceding trauma, disuse, or operation on the extremity.

Differentiate from myositis, fibrositis, and tendinitis

### General Considerations

Trauma or operation seems to be the commonest cause of this neurovascular syndrome, although the injury may have been so slight as to be overlooked by the patient. Reports of one type "shoulder-hand syndrome," have become more frequent in recent years following disuse, prolonged bed rest, and myocardial infarction.

### Clinical Findings

**A Symptoms and Signs** Pain on use of the involved extremity is first noted several weeks to months after the inciting episode. The pain is often quite severe and leads to further limitation of joint motion and deformity. Symptoms are usually aggravated by cold environment or dependency. The patient's life may be dominated by the effort to avoid the slightest trauma to the extremity.

The skin of the extremity is usually cold, moist, cyanotic, and atrophic, with loss of hair. There may be episodes of typical Raynaud's phenomenon as well as edema and tenderness, especially over various trigger points.

**B X-ray Findings** Osteoporosis of bone is commonly seen on x-ray.

### Prevention

Avoid trauma to the affected part. In the "shoulder-hand" syndrome physical therapy may be of value.

### Treatment

The symptoms usually subside spontaneously after 1-2 years, conservative therapy, consisting of keeping the affected area cool and protected from stimuli, is therefore the treatment of choice. Narcotics should be avoided if possible.

Sympathectomy (if sympathetic nerve block gives relief) is the operative treatment of choice if conservative therapy fails. Division

of the nerve distal to the site of irritation although it relieves the causalgia produces denervation of the tissue and therefore often other more distressing symptoms Spinothalamic tractotomy is a desperate measure not uniformly successful, and reamputation of the stump is usually followed by recurrence of symptoms in the revised stump

### Prognosis

Marked emotional and physical disability may occur Spontaneous remissions are rare if treatment fails the prognosis for a useful life is poor

## ARTERIOVENOUS FISTULAS

### TRAUMATIC ARTERIOVENOUS FISTULAS OF THE EXTREMITIES

#### Essentials of Diagnosis

- Increase in size of an extremity and elevation of temperature of the part occurring after injury
- Continuous thrill and bruit ( 'machinery-like murmur') over fistula
- Signs of venous insufficiency often present
- Signs of high-output cardiac failure may be present

Differentiation must be made primarily from chronic venous insufficiency Chronic venous insufficiency secondary to varices or phlebitis is not associated with a warm extremity and there will be no bruit Ulcers in chronic venous insufficiency are located in the region of the medial malleolus whereas the ulceration occurring with arteriovenous fistulas is more commonly in the distal part of the foot

#### General Considerations

Acquired arteriovenous fistulas of the extremities are almost always secondary to penetrating wounds and are therefore most often seen in men They may occur anywhere in the extremities or in the brain chest abdomen, or wherever an artery and vein are in close proximity to each other

#### Clinical Findings

**A Symptoms and Signs** The patient will give a history of penetrating injury and will

usually note that in the ensuing years the limb has become larger and warmer than its mate and that varicose veins have developed in the affected part Increased pigmentation and even stasis ulceration may occur

The outstanding sign is a 'machinery-like murmur over the fistula which is heard throughout systole and diastole with accentuation during systole The murmur may also be associated with a thrill and can usually be heard promptly after the injury causing the fistula Skin temperature is increased and signs of venous insufficiency are common as a result of the increased venous pressure caused by direct communication between the artery and vein Venous pulsations can often be seen Signs of cardiac enlargement and failure are not common but may be present especially in large fistulas of long duration Pulse pressure is often markedly widened When the fistula is closed by digital pressure a sharp decrease in pulse rate occurs (Branham's sign)

**B Laboratory Findings** The venous pressure in the region of the fistula is increased Total blood volume may be increased Oxygen saturation in the veins of the affected extremity will be higher than in those of the opposite member

**C X-ray Findings** Arteriography is of great help in some cases

#### Treatment

Repair of the defect should be carried out soon after the initial wound has healed and the tissue reaction has subsided in order to prevent local and cardiac complications

#### Prognosis

Prognosis depends greatly on the location size and duration of the lesion The disease may be relatively benign or may cause a fatal secondary congestive heart failure

See reference at end of next discussion

## CONGENITAL ARTERIOVENOUS FISTULAS

### Essentials of Diagnosis

- Increased size of an extremity and elevation of temperature of the part
- Varicose veins are almost always present
- Thrill and bruit are usually not present
- Birthmarks are common

### General Considerations

Most congenital arteriovenous fistulas occur in the extremities but they may occur in other regions (e.g., in the lung in hereditary hemorrhagic telangiectasia). The abnormal communications between arteries and veins are usually small and multiple and may occur anywhere in the extremity.

### Clinical Findings

**A Symptoms and Signs** These are much the same as in traumatic fistulas, but there will be no history of trauma and symptoms often occur in early life. There is enlargement of the limb which is warmer than the unaffected extremity. Stasis pigmentation and ulceration may occur. Various birthmarks are common, and varices are usually noted early.

Thrills or bruits are rarely present since the arteriovenous communications are generally between small vessels. Except for these differences, and the fact that cardiac enlargement and failure are generally absent, the signs are the same as in traumatic fistulas (see above).

**B Laboratory Findings** As in traumatic fistulas (see above).

### Treatment

Surgical correction is seldom possible. In rare cases of single fistula or where the abnormality is confined to a readily accessible area, division of the communication may be feasible. Proximal ligation of the largest artery involved is usually not successful and may be dangerous.

When the fistulas are present in the lower extremities elastic bandages or stockings may prevent flow of blood into the superficial veins and thus control secondary varicose veins.

### Prognosis

Because in most instances the arteriovenous communications are multiple, surgical

therapy often fails and the prognosis for restoration of a normal limb is not good. The prognosis for life is excellent since there are essentially no serious complications. Brain abscess, often due to *Actinomyces*, may complicate pulmonary arteriovenous fistula.

Keeley, J. L., Schairer, A. E., & I. G. Pesek. Peripheral arterial aneurysms and arteriovenous fistulae. *S. Clin. North America* 40: 97-110, 1960.

Muenster, J. J., Graettinger, J. S., & J. A. Campbell. Correlation of clinical and hemodynamic findings in patients with systemic arteriovenous fistulas. *Circulation* 20: 1079-88, 1959.

## DISEASES OF THE AORTA

### THORACIC & ABDOMINAL AORTIC ANEURYSMS

#### Essentials of Diagnosis

- Pain in region of dilated artery or symptoms of pressure on neighboring structures (or both)
- An expansile pulsating mass with associated systolic bruit
- X-rays may reveal calcium in the wall of the enlarged aorta or destructive changes in adjacent bony structures
- Symptoms may be entirely lacking

Aneurysms of the thoracic aorta must be differentiated from intra-thoracic tumors, pulmonary artery aneurysms, and poststenotic dilatation of the pulmonary artery. Chest x-ray and fluoroscopy will usually make the differentiation. Abdominal aneurysm must be distinguished from other intra-abdominal tumors.

#### General Considerations

Aneurysms of the thoracic aorta are most often secondary to syphilitic involvement of the vessel but about 20% are caused by atherosclerosis. With the decreasing incidence of syphilis, relatively more atherosclerotic thoracic aneurysms are now being recognized. Trauma is a rare cause of these aneurysms. Thoracic aneurysms are more common in men by a ratio of 4:1.

Abdominal aortic aneurysms and aneurysms of the peripheral arteries are primarily due to atherosclerosis, although trauma is not an infrequent cause of peripheral aneurysms. These are all more common in the older age group and in men.

### Clinical Findings.

**A. Symptoms and Signs** Patients with aneurysms of the thoracic aorta often have no symptoms, but if the aneurysm enlarges rapidly or attains a large size it may encroach on surrounding structures. When this happens there may be substernal pain, symptoms of superior vena cava obstruction, dysphagia, dyspnea, hoarseness, or a brassy cough. Aneurysms of the abdominal aorta may also be asymptomatic or may cause diffuse abdominal pain or palpitation in the abdomen. Similar symptoms may be noted in aneurysms of the femoral, popliteal, subclavian, axillary, or brachial arteries.

A tracheal tug may be noted. Thoracic aortic aneurysms may cause dullness to percussion over the upper thorax. A systolic bruit over the aneurysm as well as a tympanic aortic second sound may be noted on auscultation, but physical signs are often absent.

Other aneurysms are diagnosed primarily by noting an expansile pulsating mass in the region of the involved artery, often with a systolic bruit in the same area.

**B. X-ray Findings** Fluoroscopy and x-rays of the chest are the most valuable procedures in the diagnosis of thoracic aneurysms, often showing a mass with calcification in its wall. Aortography may help in the diagnosis, but this is rarely necessary.

### Treatment.

Since thoracic aortic aneurysms are usually progressive in size and in symptoms and finally rupture, surgical resection is the treatment of choice. Large sacular aneurysms with narrow necks are removed at the neck with no interruption of blood flow, however, sacular and fusiform aneurysms require interruption of the blood flow, removal of the aneurysm, and replacement by means of an aortic graft. Interruption of the blood flow is accomplished by means of extracorporeal circulation or shunting, with associated hypothermia.

The treatment of large abdominal aneurysms is resection in all cases, in an aneurysm smaller than 7.5 cm, in diameter, especially if the patient has other vascular disease, conservative therapy may be indicated. Treatment of peripheral aneurysms is resection and replacement by grafting.

### Prognosis.

The prognosis of aneurysms of the thoracic aorta is poor, and death is generally due to rupture of the aneurysm into one of the structures of the thoracic cavity.

Death from rupture of an abdominal aortic aneurysm is not uncommon, and the sudden onset of abdominal pain in the region of the aneurysm should alert the physician to this grave complication.

Aneurysms in the extremity may be relatively benign, but complications may lead to loss of limb or even life. The commonest complications are distal embolization from thrombi in an aneurysm, leaking of the aneurysm, and pressure on neighboring veins and nerves by the aneurysm or hematoma.

Roberts, B., Danielson, G., & W.S. Blake-more: Aortic aneurysm. Report of 101 cases. *Circulation* 15 483-81, 1957.

Schatz, I.J., Fairbairn, J.F., & J.L. Juergens: Abdominal aortic aneurysms; reappraisal. *Circulation* 26 200-5, 1962.

## DISSECTING ANEURYSM

### Essentials of Diagnosis

- Sudden severe chest pain with radiation to back, abdomen, and extremities
- Symptoms of shock almost invariably present
- Other signs and symptoms of dissection due to obstruction of orifices of branches of aorta
- History of hypertension nearly always present
- Dissection occurs primarily in males.

### General Considerations.

Cystic medial necrosis is the underlying pathologic finding in most cases. Rupture of the intima, which is most often through an atherosclerotic plaque, is followed by dissection of the medial layer of the aorta. It may continue both up and down the aorta and involve some of its branches. There may be external rupture and sudden death, or internal rupture back into the lumen of the aorta.

Hypertension is present in the majority of patients, usually middle-aged males. The disorder is common in patients with Marfan's syndrome, and occurs occasionally during pregnancy or with coarctation of the aorta.

### Clinical Findings

**A. Symptoms and Signs** The onset is usually sudden, with severe agonizing, tearing pain, usually in the anterior chest. The pain



may radiate to the head, neck, back, abdomen and lower extremities, and may do so in an orderly, progressive fashion. Shock is almost always present, but in spite of this the BP is often elevated (i.e., shock due to relative fall in BP). Obstruction of the carotid arteries may lead to convulsions, hemiplegia, or coma and, if the orifices of the vessels supplying the spinal cord are involved, paralysis of the lower extremities. Obstruction of branches of the aorta supplying the extremities is frequent and may lead to difference in BP in the arms, absent pulsations in an extremity, or signs of acute arterial occlusion. An aortic diastolic murmur due to functional insufficiency caused by retrograde dissection may be noted. Fever is commonly present.

**B. Laboratory Studies.** Leukocytosis is found frequently, as is rapidly progressing anemia also if external rupture occurs. ECG changes are often absent unless dissection involves a coronary ostium.

**C. X-ray Findings.** Chest x-rays may reveal widening of the aortic shadow as compared to a previous roentgenogram. In subjects surviving the initial episode and in whom surgical treatment is contemplated, aortography may be indicated.

#### Differential Diagnosis

Dissecting aneurysm is most commonly confused with acute myocardial infarction. The diagnosis of dissection is favored by the presence of hypertension in association with pain and shock, the persistence of the pain in spite of narcotics, and the occurrence of the peak of intensity of the pain within seconds rather than minutes of its onset. Radiation of the pain to the lumbar region, the thighs, and hips should strengthen the suspicion of dissection, as would differences in BP and in peripheral pulsations also. The chest x-ray findings mentioned above may help in the differentiation. The usual absence of ECG changes is helpful also.

#### Treatment.

Treatment of a dissecting abdominal aneurysm is aimed at creating a re-entry from the dissection into the true lumen. Shunting of the blood or hypothermia (or both) is required to prevent spinal cord damage while the aorta is clamped. Resection and grafting should be considered if the intimal tear occurs distal to the left subclavian artery.

#### Prognosis

The prognosis in dissecting aneurysm of the aorta is grave. Approximately one-third of

those affected die suddenly. Death occurs within hours or days in another 50-60%. This is due to external rupture into the mediastinum, pericardium, or the pleural or peritoneal cavity. The remainder of patients may live for months to years. Surgical treatment with establishment of an aortic window may be of great help in the latter 2 groups.

Hirst, A. E., & others. Dissecting aneurysm of the aorta: a review of 500 cases. *Medicine* 37: 217-79, 1958.

## DISEASES OF THE PERIPHERAL VEINS

### VARICOSE VEINS

#### Essentials of Diagnosis

- Dilated tortuous veins in the lower extremities
- Varicose veins may cause no symptoms or may be associated with abnormal fatigue, localized aches, or paresthesias in the extremity.

Whenever varices are seen, arteriovenous fistulas should be considered. The history of a penetrating wound, the to-and-fro bruit, and, if necessary, oxygen saturation studies and arteriography should differentiate this condition from varicose veins. Hemangiomas and other blood vessel tumors usually are not difficult to differentiate from localized varicose veins.

#### General Considerations.

Varices may be primary (idiopathic) or secondary to venous obstruction. Primary varices develop probably as a result of a congenital weakness of the veins or their valves. They tend to occur in families, and prolonged standing seems to be an important causative factor. Obesity seems also to predispose to their appearance.

Secondary varicose veins occur most commonly following iliofemoral thrombophlebitis, but also during the later months of pregnancy and in various lesions obstructing venous return (e.g., abdominal tumors).

### Clinical Findings

**A Symptoms and Signs** Most commonly the patient presents with asymptomatic varices. There may be heaviness or fatigue of the extremity, localized pain, or night cramps. Often these symptoms seem to be on a functional basis rather than due to the varices.

Inspection usually shows brownish discoloration of the skin. There may be no secondary tissue changes even in extensive varicosities.

**B Percussion Test** Palpation with 1 hand while striking along the course of the vein with the other will outline the varicosities.

**C Trendelenburg's Test (Modified)** Place the patient supine and elevate the limb to empty the superficial vessels. Compress the greater saphenous vein proximal to the knee with a rubber tourniquet. Simple varices (due to saphenofemoral valve incompetence) below the tourniquet will remain empty for over 20 seconds and then will fill slowly from below. If the tourniquet is released suddenly the simple varicosities will fill suddenly from above. If the varicosities fill rapidly from below with the tourniquet in place the test should be repeated with the tourniquet just below the knee. Nonfilling now indicates simple varices due to saphenopopliteal valve incompetence. Rapid filling indicates postphlebotic varicosities with many incompetent perforating or communicating veins.

**D Perthes Test** This test is used to determine if the saphenous and communicating valves are competent or if deep venous obstruction is present.

**1. Technic** - With the patient standing apply a tourniquet to the thigh to occlude the superficial but not the deep veins of the leg. Require the patient to walk for 5 minutes.

**2. Interpretation** - (1) If the veins collapse the communicating veins are assumed to be competent. If the veins fill slowly ( $\frac{1}{2}$ -1 minute) when the tourniquet is removed, the saphenofemoral valve is also competent. (2) If the veins do not collapse, the valves of the communicating and saphenous veins are incompetent. The pressure in the 2 systems is equal. (3) If the veins distend and pain occurs, the deep veins are obstructed and the valves of the communicating veins may be incompetent.

### Complications

Phlebitis may occur in varices (usually a benign complication). Chronic venous insufficiency with edema, stasis dermatitis, and ulceration may occur.

### Treatment.

**A. Conservative Treatment** Although only surgery can provide prolonged relief when the saphenofemoral valve is incompetent conservative measures consisting of elastic stockings and intermittent leg elevation may be of temporary value. Conservative measures are also of value in the prevention of progression in mild cases.

The injection of varicosities with a sclerosing solution is more properly reserved for treatment of short segments that remain after surgery than for primary treatment. Only 2-3 areas should be injected at any one visit.

The technic for sclerosing consists of inserting a fine (25 gauge) needle into the varix while the leg is dependent. The leg may then be brought to a horizontal position. After it is certain that the needle is in the vein and when the vein is relatively free of blood, 1-2 ml of the sclerosing solution are injected. The needle is then withdrawn, and the sclerosing solution is held for 2-3 minutes in the area of the injection by pressure above and below the site of injection. Sodium psyllate (Synasol<sup>®</sup>) and tetradecyl sulfate with benzyl alcohol 3% (Sotradecol<sup>®</sup>) are acceptable sclerosing agents.

The recurrence rate after injection is high and complications (local reaction, infection or deep thrombophlebitis) are not uncommon.

**B Surgical Treatment** The treatment of choice is high ligation at the saphenofemoral junction with stripping of the vein and interruption of the incompetent perforators. Multiple low ligations of the major channels, with interruption of the incompetent perforators, is preferred by some, but probably is not as satisfactory as ligation and stripping.

After surgery early ambulation with Unna's boots or elastic bandages is encouraged as soon as recovery from the anesthesia will permit. Standing and sitting are contraindicated. In bed the legs should be elevated.

### Prognosis

The prognosis in primary varicose veins is extremely variable, depending upon the presence or absence of chronic venous insufficiency. In secondary varices the underlying causative disorder is the important factor. However, even with removal of the primary causative factor, secondary changes due to long-standing insufficiency may not regress.

Montgomery, H., & H. A. Zintel. Clinical study and treatment of varicose veins. *Circulation* 10:442-50, 1954.

## THROMBOPHLEBITIS OF SUPERFICIAL VEINS

### Essentials of Diagnosis

- Red, painful, tender raised areas on the skin, usually in linear distribution along the course of visible veins
- Often involves several areas
- No constitutional reaction

The linear rather than circular nature of the lesion, the lack of ulceration, and the distribution along the course of a superficial vein serve to differentiate superficial phlebitis from erythema nodosum, erythema induratum, panniculitis, and fibromyositis

### General Considerations.

Superficial phlebitis may follow trauma to the veins, either chemical (e.g., following I.V. injections) or mechanical (e.g., phlebitis following injuries). It often occurs in varicose veins. A special type of superficial phlebitis is that occurring with visceral carcinoma (especially with carcinoma of the body and tail of the pancreas, but also with carcinoma of the lung, stomach, colon, prostate, or ovary); it is thought to be secondary to increased blood coagulability. It may be the earliest sign of carcinoma and tends to be recurrent. Superficial phlebitis may occur following surgery, in the postpartum period, or in any disorder requiring prolonged bed rest or immobility. Superficial phlebitis is a not uncommon sign of thromboangiitis obliterans, and may also be seen with certain blood dyscrasias. "Idiopathic recurrent superficial phlebitis," which occurs primarily in healthy young men, often affects large superficial veins and is diagnosed primarily by exclusion of the other disorders capable of causing superficial phlebitis. "Phlebotrombosis" is the clinical term for the presence of a clot in a vein which has not caused an inflammatory reaction.

### Clinical Findings.

Painful raised areas on the skin of the extremities are the major symptoms of superficial phlebitis. Firm, tender, inflamed cords will be noted along the course of small superficial veins or along the great saphenous, small saphenous, or larger veins in the arms. These are often multiple, slightly raised lesions. The inflammatory reaction subsides in 1-2 weeks, but the firm cord may remain for a much longer period. Edema is absent.

### Treatment.

If the process is well localized and not near the saphenofemoral junction, local heat and bed rest with the leg elevated are usually satisfactory. Phenylbutazone (Butazolidin®), 100 mg t.i.d. for 5 days, will aid in the resolution of the inflammatory process, but is contraindicated in individuals with peptic ulcer.

If the process is very extensive or shows a tendency to proceed upward toward the saphenofemoral junction, or if it is in the proximity of the saphenofemoral junction initially, ligation and division of the saphenous vein at the saphenofemoral junction is indicated.

Anticoagulation therapy is not indicated unless there seems to be a rapid progression of the disease or if involvement of the deep system seems imminent.

### Prognosis

The course is generally benign and brief, and the prognosis depends on the underlying pathology. Phlebitis of a saphenous vein occasionally extends to the deep veins, in which case pulmonary embolism may occur.

## THROMBOPHLEBITIS OF DEEP VEINS

### Essentials of Diagnosis

- Pain in the involved extremity
- Edema, superficial vein dilatation, tachycardia, fever
- Calf tenderness and positive Homans sign

Differentiate phlebitis of the calf veins from fibrositis, sciatica, muscle strain, and rupture of a vein in the calf. Iliofemoral phlebitis may be confused with acute arterial occlusion and lymphangitis or cellulitis, but the presence of arterial pulsations and the lack of skin inflammation usually point to phlebitis.

### General Considerations.

Thrombophlebitis of the deep veins most commonly occurs following delivery, surgery, or trauma. Stasis of blood following prolonged bed rest or immobilization is believed to be a major causative factor. When deep phlebitis occurs in infectious diseases and heart disease, the same factor is probably at work. Deep phlebitis may also be seen in

marked obesity or with the various carcinomas listed under superficial phlebitis, and may rarely be of the idiopathic recurrent type

### Clinical Findings

The primary symptom of thrombophlebitis of the deep veins is pain. If the popliteal or iliofemoral veins are involved, swelling of the leg will be noted. The onset is generally acute and the pain moderate.

Phlebitis of the calf veins is characterized by tenderness in the calf muscles, particularly on bilateral pressure. There is no edema, and no constitutional symptoms or signs occur. Iliofemoral phlebitis, on the other hand, is characterized by edema of varying degrees. Fever is usually present but is rarely over 38°C (102°F). Tachycardia is not uncommon. Tenderness in Scarpa's triangle, dilated superficial veins, and diffuse enlargement of the limb make up a characteristic triad. Homans' sign (pain behind the knee when the foot is forcibly dorsiflexed) may or may not be present in thrombophlebitis of the deep veins. The symptoms and signs in axillary or subclavian phlebitis are similar to those described for iliofemoral thrombophlebitis.

### Complications

The major complication of deep phlebitis is pulmonary embolism. Chronic venous insufficiency and varicose veins may occur.

### Prevention

**A Early Ambulation.** Prolonged bed rest or inactivity should be avoided, especially in elderly patients. Have the patient up and about as soon as possible after operation or acute illness. Walking a few steps is preferable to sitting for half an hour or more in a chair.

**B Bed Exercises.** If bed rest is necessary, passive or active bed exercises should be instituted as soon as possible and should be continued as long as the patient must remain in bed. These consist of active or passive flexion of the toes, ankles, knee, and hips, repeated 5-10 times every hour while awake.

**C Movement in Bed.** Keep the bedclothes loose so the patient can move his legs freely.

**D Elevation and Compression.** Elevation of the foot of the bed 10-15 cm. (4-6 inches) and wrapping the legs from the toes to just below the knees with elastic bandages will usually promote venous return.

**E. Routine Prophylactic Use of Anticoagulants.** In elderly patients who cannot perform

any of the above exercises, anticoagulants may be of value. In general, however, the routine prophylactic use of anticoagulants is not advised.

### Treatment.

**A Anticoagulant Therapy.** As soon as the diagnosis of venous thrombosis is made, anticoagulant therapy must be started at once. **Note:** The prothrombin level and Lee-White clotting time must be determined first.

1. **Heparin.** For immediate effect, administer 25-75 mg ( $\frac{3}{8}$ - $\frac{1}{4}$  gr.) I.V., and repeat every 6 hours, determining the Lee-White clotting time before each dose, until the prolonged effect of the subcutaneously administered material has taken effect (persistent prolongation of the clotting time).

Concomitantly with the I.V. dosage, inject a highly concentrated aqueous solution of heparin (200 mg per ml) slowly through a No. 25 needle into the subcutaneous fat 2.5-5 cm (1-2 inches) below the posterior iliac crest. Average doses are as follows:

100 lb patient - 100 mg ( $\frac{1}{2}$ gr.)
every 12 hours
150 lb patient - 125 mg ( $\frac{2}{3}$ gr.)
every 12 hours
175-200 lb patient - 125-150 mg ( $\frac{2}{3}$ - $\frac{1}{2}$ gr.)
every 12 hours

Check Lee-White clotting times before starting treatment and just before the next dose. If the clotting time exceeds 18 minutes defer the next dose until it falls below this level. Modify dosage as necessary. This gives a prolonged anticoagulant action. The dosage usually is repeated every 12 hours but the effect may last 18 to 36 hours.

At present the most general use of heparin is during the first stage, or from the first to the third days of anticoagulant therapy, until the oral prothrombin depressants become effective. The subcutaneous administration of heparin may be used alone without the addition of prothrombin depressants.

2. **Prothrombin depressants.** Prothrombin depressants differ in rapidity of onset and duration of effect. The actual figures are dependent upon dose, but approximate values for comparison are given in the table. Bishydroxycoumarin is probably the most widely used. None offers advantages sufficient to justify changing from a preparation with which the physician is experienced. The indications cause a greater incidence of allergic reactions, and the prothrombin response is less stable.

A good therapeutic effect has been achieved when the prothrombin activity has fallen to at

## Prothrombin Depressants

	DOSAGE (ORAL)*			Approximate Time to Peak Effect (Days)	Approximate Duration of Effect (Days)
	1st Day	2nd Day	Usual Daily Maintenance and Range		
Bishydroxycoumarin (Dicumsol <sup>®</sup> )	200-400 mg	100 200 mg	100 mg (25-150)	2-3	4
Warfarin (Coumadin <sup>®</sup> , Panwarlin <sup>®</sup> Athrombin <sup>®</sup> )	30 50 mg	10-15 mg	7 mg (5-15)	1-2	2-3
Diphenadione (Dipaxin <sup>®</sup> )†	40 60 mg	10 20 mg	7 mg (2.5-10)	2-3	10
Phenindione (Danilone <sup>®</sup> , Hedulin <sup>®</sup> )†	100 250 mg b i d	25 75 mg b i d	50 mg (12.5 75) b i d	1-2	4
Anisindione (Miradon <sup>®</sup> )†	300 mg	200 mg	75 mg (25 250)	1-2	4
Phenprocoumon (Liquamar <sup>®</sup> )	30 mg	10 mg	3 mg (1 6)	1-2	4
Acenocoumarol (Sintrom <sup>®</sup> )	16 28 mg	8-16 mg	6 mg (2-10)	1-2	2
Ethyl bis coumatate (Tromexan <sup>®</sup> )	750 900 mg. b i d	150 300 mg b i d.	300 mg (150 450) b i d	1	2

\*Only warfarin may be given I V. The oral route is almost always used. Dosages given are single daily doses unless otherwise specified.

†Indandione derivative. Allergic reactions including agranulocytosis, occur. Hepatitis may occur with phenindione.

least 30%, preferably as close to 10% as possible. At the beginning of treatment daily prothrombin activities should be determined and the subsequent dose withheld until the report is received. In well-stabilized patients weekly or even monthly determinations may be adequate.

The usual starting doses and maintenance doses of the common anti-prothrombin drugs are shown in the following chart. Patients with initial activities below 80-100% should receive smaller doses.

3. Duration of therapy varies with each case. For most patients this is about 10-14 days. Continue the therapy for about 7 days after there is no further fever or pain.

4. Treatment of bleeding and overdosage. The principal danger from anticoagulant therapy is abnormal bleeding. In bleeding due to heparin excess the coagulation time can be rapidly returned to normal by injecting 1% protamine sulfate in physiologic saline I V. Give a dose equal (mg for mg) to that of the administered heparin. The duration of action of heparin is 2 hours.

Toluidine blue, 4-6 mg /Kg slowly I V in physiologic saline, acts more slowly than protamine, but its effect lasts many hours.

Hexadimethrine bromide (Polybrene<sup>®</sup>) is an alternative heparin antagonist administered as described for protamine.

If long-acting heparin has been administered it may be necessary later to repeat the protamine.

Bleeding due to excess prothrombin depressants is more difficult to control, for the prothrombin level rises slowly after therapy is discontinued. For severe bleeding, stop the drug and do not use it again. Give a transfusion of fresh citrated blood or reconstituted plasma immediately. Give one of the following (1) Phytonadione (Mephyton<sup>®</sup>), 50-200 mg I V slowly (at rate not over 10 mg /minute by syringe or added to venoclysis of dextrose or saline) repeat every 6 hours as necessary. This acts more rapidly than synthetic vitamin K-like products (e.g., menadione). (2) Menadione sodium bisulfite (Hykinone<sup>®</sup>), 72 mg I V stat. For mild bleeding (mild nasal, hemorrhoidal, urinary oozing), stop drug and restart at lower dosage after prothrombin time rises to 20-30%, and give phytonadione (Mephyton<sup>®</sup>) 5-30 mg orally. If bleeding is not controlled or becomes more severe, give phytonadione I V as above.

If the prothrombin level drops below 10% and does not rise above 25-30% in 2 days after discontinuing medication, overdosage of prothrombin depressant must be assumed even if bleeding does not occur. Give phytonadione (Mephyton<sup>®</sup>) 5-30 mg orally. When prothrombin rises, the drugs may be given again.

**B Vein Ligation** Vein ligation is recommended for any case in which anticoagulant therapy is contraindicated. These are patients with purpura, open ulcers, drainage tubes, certain patients with renal or hepatic disease, and patients being prepared for CNS surgery. Vein ligation is also indicated if there are signs of propagation of the thrombus. If emboli continue to occur during anticoagulant therapy, or if septic phlebitis is present.

**C General Measures** The patient should be at bed rest with the foot of the bed elevated 10-15 cm (4-6 inches). An elastic bandage is applied snugly from the foot to above the knee or mid-thigh to keep veins collapsed. Do not obstruct arterial circulation. Check pulses. Rewrap every 6 hours.

1. **Exercise** - As soon as treatment is started, allow free movement and exercises in bed. If the leg is in a cast, the patient may exercise by tensing and relaxing the muscles.

2. **Ambulation** - As soon as the acute pain subsides (or, if no pain is present, as soon as therapy is instituted), the patient must be made ambulatory (unless other systemic conditions prevent this). During this time an elastic bandage should be worn. The time out of bed and walking is increased every day. The elastic bandage should be worn for about 3 weeks after full ambulation has been achieved.

### Prognosis

With adequate treatment the patient usually returns to normal health and activity within 1-2 weeks. The prognosis is excellent unless pulmonary embolism occurs.

Byrne, J. J. • Phlebitis. A study of 979 cases at the Boston City Hospital. *J. A. M. A.* 174:113-8, 1960.

Fuller, C. H., Robertson, C. W. & R. H. Smithwick. Management of thromboembolic disease. *New England J. Med.* 263:983-7, 1960.

Thomas, A. B., Scallen, R. W., & I. R. Savage. The prophylactic value of long-term anticoagulant therapy. *Circulation* 21:354-62, 1960.

## CHRONIC VENOUS INSUFFICIENCY

### Essentials of Diagnosis

- Ankle edema is the earliest symptom.
- Stasis pigmentation, dermatitis, and induration occur later.
- Internal malleolar ulceration is common.

Differentiate from other conditions causing edema of the legs (e.g., heart failure, lymphedema, lipedema) and from the various diseases producing leg ulcers (e.g., chronic arterial insufficiency, erythema induratum, hematologic disorders).

### General Considerations

The syndrome of chronic venous insufficiency results from stasis of venous blood flow. The primary causative disorders are obstruction of the main veins by phlebitis, tumors, or external pressure from other sources, varicose veins of long standing, and arteriovenous fistulas. Although not a primary etiologic factor, trauma frequently initiates the various complications (principally ulceration).

### Clinical Findings

Edema around the ankle region is usually the first symptom. There may be mild pain on prolonged standing, which is usually relieved by rest. Pruritus around the ankle may be noted, and ulceration may occur.

The edema is most often around the ankle but may involve the foot. After it has been present for some time, hemosiderin pigmentation around the ankle often is present. Dry scaling eczematoid dermatitis in this region is also a common manifestation. With persistence of edema, subcutaneous fibrosis and a low-grade inflammatory reaction occasionally occur in the ankle region, this has been called "chronic indurated cellulitis." Ulceration when present, usually occurs in the region of the internal malleolus, but may occur laterally in rare cases. Ulceration may heal readily or become chronic and recurrent.

### Differential Diagnosis

The edema of congestive failure is usually bilateral and symmetric and may involve the sacral region, other signs of congestive failure should make the differentiation from venous insufficiency rather simple.

The nephrotic syndrome causes widespread edema with urinary findings.

Lymphedema causes a brawny edema which does not subside easily with elevation. The other signs of venous insufficiency (e.g., pigmentation and ulceration) are absent in lymphedema.

Lipedema occurs bilaterally in women with marked obesity (especially about the pelvis), rarely progresses, and is not associated with ulceration, varices, or pigmentation.

Arteriovenous fistulas are characterized by a bruit and thrill and a history of injury; arteriographic studies are characteristic.

Ulcers of chronic arterial insufficiency are much more painful than those of venous insufficiency. They generally occur on the toes or the foot and extremity pulsations are absent.

Erythema induratum begins as painful nodules followed by ulceration. This is usually bilateral and symmetric and the ulcers occur primarily on the posterior surface of the lower part of the leg.

Numerous other leg ulcers (e.g. those of trauma, sickle cell anemia and fungal infections) can usually be differentiated from venous insufficiency by absence of varicose veins, congestion of the skin and edema.

### Complications

Secondary infection of an ulceration and extensive ulceration may occur. The ulceration may require grafting.

### Treatment

The accumulation of protein-rich fluid is the main cause of the more serious manifestations of the postphlebotic syndrome. If edema is conscientiously avoided, these may be prevented.

**A Control Edema.** The patient should sleep with the foot of his bed on 10 cm (4 inch) blocks, wear well-fitted (made to order) heavy-duty elastic stocking below the knee with fitted heel and take 3-4 20 minute rest periods during the day with the feet elevated 15-20 cm (6-8 inches) above heart level.

**B Control Infection.** Control of dermatophytosis and onychomycosis is essential. Castellani's dye to toes and nails once or twice a week is probably the best control measure.

**C Eczema and Ulceration.** Once these signs appear, elastic support is not adequate. A carefully fitted semi-rigid boot of the Unna's paste type will heal most ulcers in 1-4 months. Boots may be applied with tape and sheet cotton Viscopaste® or Gauztex®. The patient continues his usual activities. These boots should be applied with firm even pressure over the leg without irregularities which may cause further damage to the skin. They must be changed every 1-2 weeks depending upon drainage but once the ulcer is healed or drainage is minimal it can be left on as long as 4-6 weeks.

Viscopaste® bandage is an Unna's paste type bandage 3 1/2 inches wide impregnated with gelatin and zinc oxide. The Gauztex® bandage is a 3 inch bandage impregnated with a non-allergenic self-adhering compound.

The bandage should extend from the base of the toes include the heel and continue to a point immediately below the bend of the knee. A thin layer of cotton sheeting or gauze is used to pad the Achilles tendon and the dorsum of the foot. An extra layer of cotton or gauze and sometimes a rubber sponge 1/2 inch thick is placed over the ulcer. Special ointments especially antibiotic preparations are not necessary. The bandage is started with a horizontal turn around the foot and when completed it is carried obliquely over the heel and then back around the foot. After the heel has been adequately covered the bandage is carried up the leg. No attempt should be made to apply it as a continuous spiral. It should be allowed to follow its own course without pleating and should be cut frequently if necessary so that bandaging may be recommended to build up a uniform thickness of paste or bandage. The bandage should be molded carefully to conform evenly to the shape of the limb.

### Prognosis

If possible the primary disorder should be treated before symptoms and signs of chronic venous insufficiency appear. Long standing edema and ulceration may not be reversible following correction of the primary lesion.

De Takats G. Postphlebotic syndrome  
J A M A 164 1851-7 1957

## SUPERIOR VENA CAVA OBSTRUCTION

### Essentials of Diagnosis

- Dilated veins of the chest, neck, arms and head
- Edema and cyanosis of the face and upper extremities
- Elevated venous pressure in the upper extremities with normal venous pressure in the lower extremities is diagnostic

Differentiation from diseases causing generalized edema (e.g. congestive heart failure and nephrosis) is usually not difficult since the symptoms and signs of superior vena cava obstruction are limited to the head and upper extremities.

### General Considerations

The causes of the superior vena cava syndrome are neoplasms (primarily carcinoma of the lung), aortic aneurysms, tuberculous medi-

astinitis pyogenic infection of unknown origin  
thrombophlebitis and constrictive pericarditis

### Clinical Findings

**A Symptoms and Signs** The earliest symptoms are often due to cerebral congestion headache vertigo and occasionally mental confusion Edema of the head neck and arms may be noted as well as prominence of the eyes Symptoms of the underlying disorder often overshadow those of the venous obstruction

The signs are confined to the head and upper extremities Early there may be dilated venules over the chest but as the process progresses large vein distention is present in the arms neck and head Cyanosis and edema are often noted in the face and arms The signs are exaggerated by stooping bending forward and physical exercise Suffusion of the conjunctivas and exophthalmos is also common

**B Laboratory Findings** Venous pressure elevation in the arms with normal pressure in the leg veins is diagnostic

### Treatment

Treatment depends upon the underlying disease (e.g. antituberculosis chemotherapy nitrogen mustard for lymphomas) A vein graft can be tried in the affected area if the underlying disease can be controlled Experience with this procedure has been disappointing however

### Prognosis

The prognosis depends upon the nature of the obstructive lesion It is especially bad when malignancy or aortic aneurysm is the cause Even with mediastinitis and primary thrombophlebitis the mortality rate is high

- Failor H J Edwards J E & C H Hodgson  
Etiologic factors in obstruction of the superior vena cava a pathologic study Proc Staff Meet Mayo Clin 33 671 8 1958  
McIntire F T & E M Sykes Jr Obstruction of the superior vena cava a review of the literature and report of two personal cases Ann Int Med 30 925 60 1949

## DISEASES OF THE LYMPHATIC CHANNELS

### LYMPHANGITIS

#### Essentials of Diagnosis

- Red streaks along an extremity which is hot and enlarged
- Chills common at onset
- Fever usually high
- Lymphadenitis present

#### General Considerations

Lymphangitis generally follows bacterial entry through the skin although an obvious portal of entry may be absent It commonly occurs secondary to trauma trichophytosis or chronic ulceration The usual organism is the streptococcus Spreading lymphangitis implies poor localization of the infection and before the antibiotics were available was of serious prognostic significance

#### Clinical Findings

**A Symptoms and Signs** The onset of symptoms is usually sudden following some type of local bacterial invasion The patient complains of malaise anorexia sweating shaking chills and fever usually to 39.4-40°C (103-104°F) Slightly indurated red tender streaks will be noted and the regional lymph nodes soon become enlarged and tender The pulse rate will be increased

**B Laboratory Studies** Leukocytosis is usually present Blood cultures may be positive

#### Differential Diagnosis

Lymphangitis in the lower extremity is most often confused with iliofemoral thrombophlebitis In both diseases the limb is enlarged but in phlebitis there is tenderness in Scarpa's triangle and there are dilated superficial veins Chills and fever greater than 38.9°C (102°F) are rare and the red streaking and local lymphadenopathy are never seen in iliofemoral thrombophlebitis

#### Treatment

Place the patient at bed rest and immobilize the affected part Give systemic anti-infective therapy The infection is usually due to streptococci and penicillin must be given without delay Erythromycin may also be used Give analgesics as necessary



Apply local heat in the form of warm moist compresses or soaks

### Prognosis

With the proper therapy this disorder can be adequately controlled within 4-6 days. Septicemia is rarely seen unless treatment has been delayed.

Shick, R. M. Recurrent lymphangitis and cellulitis of the extremities. *M. Clin. North America* 49:1039-98, 1949

## LYMPHEDEMA

### Essentials of Diagnosis

- Painless edema of one or both lower extremities primarily in young females
- Initially, pitting edema which becomes brawny and often nonpitting with time
- Ulceration and varicosities do not occur
- May have associated lymphangitis and cellulitis

Differentiation from generalized systemic disease causing edema (e.g. nephrosis or heart failure) is generally not difficult. Differentiation must also be made from arteriovenous fistulas and chronic venous insufficiency. Venous insufficiency may be difficult to differentiate in its early stages from the early stages of lymphedema but a history of edema following delivery surgery, or prolonged illness and rapid onset with dilated superficial veins and pain in the extremity favor venous insufficiency.

### General Considerations

Primary lymphedema occurs in 2 forms (1) congenital lymphedema, present at birth or shortly thereafter, and (2) lymphedema praecox appearing most often near puberty. The etiology of these conditions is not known although stasis of lymph flow secondary to lymphangiectasis is an important factor. Lymphedema praecox occurs generally in young females and tends to be bilateral. Important causes of secondary lymphedema are conditions causing obstruction of lymphatics (e.g. primary malignancies, local tissue injury and inflammation, and recurrent low-grade lymphangitis). Surgical extirpation of lymph nodes and x-ray therapy also may be followed by lymphedema.

### Clinical Findings

Swelling of the foot, ankle, and lower extremity is generally the first complaint. As this progresses the entire extremity may enlarge; the formerly smooth skin becomes roughened and soft edema becomes firm and nonpitting. There may be a dull heavy sensation but pain is conspicuously absent. In the inflammatory type there is usually a history of recurrent lymphangitis; each attack being followed by progression of lymphedema.

Early in the course the edema is soft and pitting on pressure is noted. Later the skin is thickened and fibrotic, with brawny nonpitting edema. Ulcers and varicosities are absent but evidence of cellulitis and lymphangitis is frequently noted. Enlarged nodes are not a part of the disease entity itself and should always lead to investigation for an underlying malignancy.

### Treatment

There is no entirely satisfactory treatment for lymphedema. Periodic elevation of the extremity, elastic bandages and massage of the leg toward the trunk are helpful in decreasing stasis. Surgical excision of edematous strips of skin down to the fascia or extensive excision with grafting is unsatisfactory both cosmetically and functionally and should be considered only in very severe chronic cases.

### Prognosis

Lymphedema praecox generally progresses gradually and marked enlargement of both legs is not uncommon although the disease may cease to progress at any point. Inflammatory lymphedema is usually unilateral, with adequate treatment of the recurrent lymphangitis the lymphedema may be halted. In these conditions the prognosis is otherwise excellent (in contradistinction to lymphedema caused by obstruction of nodes by carcinoma or lymphoma).

De Takats, G., & M. H. Evry. *Lymphedema*. Angiology 1:73-99, 1950.

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## Blood & Lymphatics

Rolph O. Wallerstein

### ANEMIAS

#### Diagnosis of Anemia.

Anemia is a common clinical finding which requires explanation. Extensive clinical and laboratory investigations are sometimes required to determine the cause. The answers to the following 4 fundamental questions are always relevant to a complete evaluation of the anemia patient: (1) Is there evidence of iron deficiency? (2) Is the anemia megaloblastic? (3) Is there evidence of hemolysis? (4) Is the bone marrow hypoplastic?

Iron deficiency must be considered in all anemias of obscure origin - regardless of red cell morphology. Determination of marrow hemosiderin is the most reliable technic, marrow hemosiderin is always absent in iron deficiency anemia and is normal or increased in all other forms. Determination of serum iron and total iron-binding capacity is almost as valuable. The combination of low serum iron and elevated total iron-binding capacity is seen only in iron deficiency anemia. If these tools are not available, recourse must be had to obtaining a history of blood loss or evidence of it by stool guaiac determination.

The diagnosis of moderately severe megaloblastic anemia (fewer than 3 million red cells/cu. mm.) can always be made by examination of the blood and bone marrow. The blood will show oval macrocytes and hypersegmented granulocytes, and the bone marrow is characterized by megaloblasts.

The major hemolytic disorders, regardless of type, have in common: reticulocytosis, slightly increased serum bilirubin (indirect), and an increased number of nucleated red cells in the marrow.

In hypoplastic anemia the bone marrow is fatty and there are relatively few nucleated red cells. Tissue sections made from the marrow aspirate and stained with hematoxylin and eosin are best for demonstrating the characteristic architecture of a hypoplastic bone marrow.

In any case of undiagnosed normocytic normochromic anemia which does not fall into the above 4 groups, the following causes must be considered: infection, azotemia, malignancy, myxedema, and liver disease.

### IRON DEFICIENCY ANEMIA

#### Essentials of Diagnosis.

- Pallor, lassitude.
- Hypochromia, microcytosis, RBC less reduced than hemoglobin.
- Serum iron low, total iron-binding capacity increased.
- Bone marrow hemosiderin absent.
- Blood loss usually occult.

Iron deficiency anemia is the only anemia in which hemosiderin is absent in bone marrow, in all other types of anemia iron is present in bone marrow in normal or increased amounts. In thalassemia minor (which is also manifested by a hypochromic, microcytic anemia) the red cells are smaller and have a more abnormal appearance (for a given degree of anemia), the red count may be above normal and the hemoglobin is rarely below 9 Gm/100 ml., and the bone marrow hemosiderin, serum iron, and total iron-binding capacity are normal.

#### General Considerations.

Iron deficiency anemia in the adult is almost always due to blood loss. Excessive menstrual flow and gastrointestinal bleeding (due to hiatus hernia, gastritis, peptic ulcer, polyps, malignancy, or hemorrhoids) are the principal causes. Gastrointestinal bleeding is usually chronic and occult.

A normal daily diet contains 12-15 mg. of iron of which 5-10% (0.6-1.5 mg.) is absorbed (although more iron is absorbed in iron deficiency anemia). Because less than 1 mg. of

iron is excreted normally per day normal persons are in positive iron balance Chronic bleeding of as little as 2-4 ml of blood per day may lead to a negative iron balance and iron deficiency anemia

### Clinical Findings

**A Symptoms and Signs** In addition to symptoms of the primary disease (if any) symptoms due to anemia may be present easy fatigability dyspnea palpitation angina and tachycardia Waxy pallor brittle hair and nails smooth tongue ctenosis and dysphagia are late findings

**B Laboratory Findings** The hemoglobin may fall to as low as 3 Gm / 100 ml but the RBC is rarely below 2.5 million/cu mm and the red cells are usually hypochromic and microcytic but in approximately 20% of adults the red cells do not look abnormal Reticulocytes and platelets are normal or increased The WBC is normal

Serum iron and total iron binding capacity should be determined in doubtful cases Serum iron is usually below 30 mcg / 100 ml (normal is 80-150 mcg / 100 ml ) total iron binding capacity is elevated to 350-500 mcg / 100 ml (normal is 250-350 mcg / 100 ml )

The most critical test is the bone marrow stain for hemosiderin stainable iron is always absent in iron deficiency anemia The bone marrow aspirate contains increased numbers of nucleated red cells the normoblasts have only scanty cytoplasm

### Differential Diagnosis

Iron deficiency anemia must be differentiated from other hypochromic microcytic anemias

**A Thalassemia Minor** See p 279

**B Anemia of Infection** (See p 282 ) Red cells are normocytic and mildly hypochromic Serum iron is low but total iron binding capacity is also decreased Bone marrow hemosiderin is present

**C Sideroachrestic Anemias** This is a group of rare hypochromic microcytic anemias often familial characterized by high serum iron many erythrocytes containing nonhemoglobin iron hemosiderosis and usually some splenic enlargement

**D Some Hemoglobinopathies** All hemoglobin abnormalities involving the thalassemia gene are microcytic and hypochromic The red cells in hemoglobin E disease may be quite

small The diagnosis is made by hemoglobin electrophoresis

### Complications

There may be severe dysphagia (Plummer Vinson syndrome) Iron deficiency anemia may be the presenting finding in gastrointestinal cancer In patients with heart disease severe anemia may precipitate angina pectoris or congestive heart failure

### Treatment

Iron is specific for this type of anemia It should be started as soon as an etiologic diagnosis has been made Transfusions are rarely needed

**A Oral Preparations and Dosages** The maximum absorption is considered to be about 25 mg / day Give one of the following (1) ferrous sulfate 0.2 Gm (3 gr ) t i d after meals or (2) ferrous gluconate 0.3 Gm (5 gr ) t i d after meals Oral iron should be continued for 3 months after hemoglobin values return to normal in order to replenish iron stores

Many other iron salts and chelates often mixed with other metals or vitamins are promoted but none are more useful in iron deficiency anemia than ferrous sulfate The degree of gastrointestinal irritation and the amount absorbed are functions of the iron content of the salt or complex

**B Parenteral Iron** The indications are intolerance to oral iron refractoriness to oral iron (poor absorption) gastrointestinal disease precluding the use of oral iron and replacement of depleted iron stores when oral iron fails Parenteral iron should be given only in the amounts necessary to correct the deficiency Calculate the total dosage as follows 250 mg for each Gm of hemoglobin below normal (Normal men 14-16 Gm women 12-16 Gm )

Iron dextran complex (Imferon®) for I M use contains 5% metallic iron (50 mg / ml ) Give 50 mg (1 ml ) stat and then 100-250 mg I M daily or every other day until the total dose has been given Inject deeply with a two inch needle into the upper outer quadrant of the buttock using the Z technic (pulling the skin to one side before inserting the needle) to prevent leakage of the solution and discoloration of the skin Imferon® may also be given I V

### Prognosis

Following iron therapy all the signs and symptoms of iron deficiency anemia are reversible unless blood loss continues Bleeding

in excess of 500 ml./week over a period of weeks or months probably cannot be treated by iron medication alone.

- Beutler, E.: Clinical evaluation of iron stores  
*New England J. Med.* 256:692-7, 1957.  
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## PERNICIOUS ANEMIA (Addisonian Anemia)

### Essentials of Diagnosis.

- Anorexia, dyspepsia, smooth, sore tongue,
- Constant, symmetric numbness and tingling of the feet
- Pallor and a trace of jaundice.
- Oval macrocytes, pancytopenia, hypersegmented neutrophils
- Megaloblastic bone marrow.

The diagnosis of a megaloblastic anemia can be based with confidence upon the blood and bone marrow examinations alone if there is at least a moderate degree of anemia, i.e., RBC below 3 million/cu. mm. Although large red cells are not seen exclusively in the megaloblastic anemias, their oval appearance is characteristic, as are the hypersegmented white cells and the megaloblasts of the marrow.

### General Considerations.

Addisonian pernicious anemia is a conditioned vitamin B<sub>12</sub> deficiency which is due not to a dietary lack but to an absorption defect. Intrinsic factor, an enzyme secreted by the gastric mucosa which facilitates absorption of vitamin B<sub>12</sub>, is absent. This absorption occurs mostly in the region of the ileum, in the presence of calcium and at a pH of 5-7. The intrinsic factor defect is uncommon in persons under 35, it is most often seen in individuals of Scandinavian, English, or Irish extraction. The predisposition to pernicious anemia is probably inherited as a single dominant autosomal factor.

Rarer forms of vitamin B<sub>12</sub> deficiency include fish tapeworm disease, some types of intestinal malformation, and "blind loop" syndrome.

### Clinical Findings.

**A. Symptoms and Signs** Patients with pernicious anemia may tolerate their disease well, with few symptoms caused by either the anemia or the B<sub>12</sub> deficiency. Symptoms due to the anemia include easy fatigability, dyspnea, palpitation, angina, and tachycardia. Vitamin B<sub>12</sub> deficiency produces glossitis, gastrointestinal symptoms such as belching, indigestion, anorexia, and diarrhea, CNS symptoms occur in approximately 10% of patients and include constant symmetric numbness and tingling of the lower extremities, ataxia, mental disturbances, and loss of vibration sense and deep reflexes, sensory symptoms usually appear before the motor symptoms and signs.

### B. Laboratory Findings

**1 Blood** - In addition to the characteristic large oval red cells there are a few small misshapen red cells. The WBC is usually under 5000/cu. mm. The granulocytes, which constitute less than 50% of white cells, tend to be hypersegmented. Platelets usually are reduced (40-100 thousand/cu. mm.) Reticulocytes range from less than 1% to 3%. The icterus index is increased, but is rarely higher than 15 units.

**2 Bone marrow** - The bone marrow is hyperactive and is easily entered with this aspiration needle. The characteristic megaloblastic abnormalities are particularly evident in the more mature forms. Giant metamyelocytes are prominent. Megakaryocytes are hypersegmented and reduced in number. Hemocrit is increased and in the form of fine granules.

**3 Other laboratory tests** - There is no free gastric acid and very little gastric juice, even after injection of histamine. The Schilling test involves the oral administration of a small (0.5 mcg.) dose of radiocobalt-labeled vitamin B<sub>12</sub> followed two hours later by the parenteral administration of 1000 mcg. of unlabeled vitamin B<sub>12</sub>. The radioactive vitamin B<sub>12</sub> is excreted in the urine in 24 hours (normal 15-40%), but simultaneous administration of intrinsic factor increases the excretion of vitamin B<sub>12</sub> fivefold or more. The Schilling test is useful only in (1) differentiating Addisonian pernicious anemia from megaloblastic anemias due to folic acid deficiency, (2) diagnosing Addisonian pernicious anemia in remission, and (3) diagnosing defective vitamin B<sub>12</sub> absorption in patients with combined system disease before the onset of anemia.

### Differential Diagnosis.

In megaloblastic anemia due to folic acid deficiency, a history of poor diet, sometimes associated with alcoholism, is often obtained

("nutritional megaloblastic anemia") Other examples of folic acid deficiency are sprue, with a history of chronic diarrhea and abnormal tests, the megaloblastic anemia which is occasionally seen in epileptics on primidone (Mysoline<sup>®</sup>) therapy, and the megaloblastic anemia of pregnancy (frequently associated with vomiting and inadequate diet) In megaloblastic anemias due to folic acid deficiency, CNS symptoms are lacking, free gastric acid may be present, and the vitamin B<sub>12</sub> absorption test (Schilling) is normal In sprue, vitamin B<sub>12</sub> absorption may be impaired even after administration of intrinsic factor.

In the various hemolytic anemias some young nucleated red cells in the marrow may resemble megakaryoblasts, however, there are no oval macrocytes and no hypersegmented PMS's. and the reticulocytes are above 3%

#### Treatment.

Vitamin B<sub>12</sub> therapy is specific. Activities need not be restricted.

Pernicious anemia in relapse should be treated with vitamin B<sub>12</sub> (cyanocobalamin) or vitamin concentrate, 15-30 mcg I.M. 1-3 times/week until blood values return to normal. Thereafter 30 mcg. I.M. monthly is given. The patient must be impressed that the need for vitamin B<sub>12</sub> injections will continue for the rest of his life. Larger amounts are given if there is neurologic involvement but the evidence for increased benefit is not convincing.

Liver injection is now standardized in terms of its vitamin B<sub>12</sub> content and offers no advantage. Oral administration of huge doses of vitamin B<sub>12</sub> or of liver-stomach preparations is feasible but not recommended.

There is no need for special diets, hydrochloric acid, or folic acid - especially the last, which will not correct neurologic changes. Hospitalization or bed rest is not necessary unless enforced by profound anemia or neurologic symptoms.

Patients who have undergone total gastrectomy should receive maintenance doses of vitamin B<sub>12</sub> (30 mcg. I.M. monthly).

#### Prognosis.

Untreated pernicious anemia is fatal. With parenteral vitamin B<sub>12</sub> therapy the reticulocytes begin to increase on the fourth day and reach a peak between the sixth and tenth days. The magnitude of the reticulocyte peak correlates well with the degree of anemia, with an initial red count of 1 million/cu. mm., a maximum reticulocyte count of 40% may be anticipated. Normal hemoglobin values are obtained in about 6 weeks. CNS symptoms are reversible

if they are of relatively short duration (less than 6 months), but may be permanent if they have existed longer. Histamine-fast achlorhydria persists, the Schilling test remains abnormal.

Herbert, V.: The Megaloblastic Anemias. Grune & Stratton, 1959.

### FOLIC ACID DEFICIENCY

In megaloblastic anemia of pregnancy or infancy and in megaloblastic anemia due to malnutrition or antiepileptic therapy, folic acid is given only until a hematologic remission is obtained. No maintenance therapy is necessary.

A patient with sprue or malabsorption syndrome may require initial therapy with parenteral folic acid and maintenance with oral folic acid. Some of these patients have an associated vitamin B<sub>12</sub> or iron deficiency and have to be treated accordingly. Others require the addition of corticosteroids for relief of symptoms.

Folic acid is given orally or I.M., 5 mg daily. The I.M. preparation contains 15 mg/ml.

### APLASTIC ANEMIA

#### Essentials of Diagnosis.

- Lassitude, pallor, purpura, bleeding
- Pancytopenia, fatty bone marrow.
- History of exposure to an offending drug or x-ray radiation.

Among the pancytopenias, aplastic anemia is characterized by an atellular marrow and a spleen of normal size. In hypersplenism the marrow is hyperactive and the spleen is large, in myelofibrosis the marrow is fibrotic rather than fatty and the spleen is large; in pernicious anemia the marrow is hypercellular and the spleen may be slightly enlarged. Pancytopenia may be seen with aleukemic leukemia and lymphosarcoma. Proper diagnosis depends upon bone marrow aspiration.

#### General Considerations.

Aplastic anemia is characterized by pancytopenia or a selective depression of red cells, white cells, or platelets. In over half of cases

the etiology is not known. Aplastic anemia may occur as a toxic reaction to many chemicals and drugs, chloramphenicol (Chloromycetin<sup>®</sup>), benzene, and methylphenylethylhydantoin (Mesantoin<sup>®</sup>) are among the most common offenders. Hair dyes, plant sprays, insecticides, volatile solvents, large doses of antileukemic drugs, and excessive x-ray or ionizing radiation may also cause this disease. In some cases an associated thymoma is found. A congenital form with pancytopenia or severe red cell aplasia exists.

### Clinical Findings.

**A. Symptoms and Signs:** With anemia there is lassitude, pallor, fatigue, and tachycardia. With thrombocytopenia there is purpura and bleeding, with neutropenia there may be skin, mucous membrane, and systemic infections with high fever.

**B. Laboratory Findings:** The RBC may be below 1 million/cu.mm. The cells may be macrocytic. The reticulocyte count is often low, but may be normal or even slightly elevated. The WBC may be less than 2000/cu.mm. and the platelet count less than 30,000/cu.mm. The icterus index is usually below normal. The bone marrow is fatty. There are very few red cells, white cells, and megakaryocytes. Hemosiderin is present.

**Note:** Bone marrow tissue may be difficult to aspirate, and a biopsy may have to be performed before a diagnosis of aplastic anemia can be established.

### Differential Diagnosis.

In myelofibrosis the spleen and liver are enlarged; red cells vary in size and shape, bizarre and tear-shaped cells may be seen, leukocytosis is common; the platelet count may be low, normal, or even elevated, and giant platelets are common, the marrow is fibrotic rather than fatty; and evidence of extramedullary hemostopoiesis may be seen in the liver and spleen.

### Complications.

Long-term transfusion therapy may lead to development of leuko-agglutinins and hemosiderosis. Overwhelming infection secondary to the leukopenia and hemorrhage secondary to thrombocytopenia are frequently terminal events.

### Treatment.

**A. General Measures.** Eliminate exposure to suspected toxins and discontinue all unnecessary medication. No agents are known that will predictably stimulate marrow function, but the following may be tried.

1. Vitamin B<sub>12</sub>, folic acid, and crude liver extract.

2. Cobaltous chloride, 100-150 mg. orally daily for at least 3 weeks.

3. Methyltestosterone, 100 mg. orally daily, or testosterone enanthate in oil, 1-2 mg./Kg./day I.M. given twice a week.

4. Prednisolone (or other corticosteroid), 10-20 mg. 4 times daily.

5. If a thymoma is present, its removal may be considered.

**B. Transfusions:** Give preferably as packed red cells only, less than one week old. Five ml. of packed red cells/Kg. will raise the RBC by 10%. (For example, 500 ml. of red cells will raise the hemoglobin of a 50 Kg. patient by 20%, or 3 Gm./100 ml.) The average requirement for adults is 5 units (2500 ml. whole blood or 1250 ml. red cells) every 2 months. Post-transfusion hemoglobin levels of 11-12 Gm./100 ml. are satisfactory. Many patients do not have to be retransfused until the hemoglobin level falls to approximately 6 Gm./100 ml. The patient's red cells should be genotyped, i.e., as many of his red cell antigens as possible should be identified. Blood for transfusion should be as type-specific as possible to avoid antibody production against even minor blood types. The patient's serum should be tested at regular intervals for the development of antibodies. All transfusions must be Coombs-tested (see p. 268). If a febrile transfusion reaction develops, serum should be checked for leuko-agglutinins; if these white cell antibodies have developed, the buffy coats should be removed from all subsequent transfusions.

### C. Treatment of Complications.

1. **Infections** - Antibiotics should not be given prophylactically, even when leukopenia is severe. When infections occur, specific antibiotics are used. Patients must pay meticulous attention to personal hygiene and avoid exposure to infections.

2. **Bleeding** - When bleeding occurs in association with severe thrombocytopenia, prednisolone (or equivalent), 10-20 mg. orally every 8 hours, may be tried. There may be improvement of the hemorrhagic manifestations even without a rise in the platelet count. Acute bleeding episodes are sometimes successfully controlled by platelet-rich transfusions. This is best accomplished by giving fresh (less than 4 hours old) whole blood, carefully collected in siliconized bottles or plastic equipment.

3. **Hemolytic anemia** - If an associated hemolytic anemia with splenic sequestration of red cells develops, splenectomy may have to be considered.

**Prognosis**

The mortality with severe bone marrow depression is over 50% hemorrhage or overwhelming infection are the main causes of death. Some patients can be maintained on transfusions for years. Partial or complete spontaneous remission may occur.

Scott J L Cartwright, G E & M M Wintrobe. Acquired aplastic anemia. An analysis of thirty nine cases and review of the pertinent literature. *Medicine* 38 119 72 1959

**REFRACTORY NORMOBLASTIC ANEMIA**

This is a chronic moderate to severe anemia characterized by a normal reticulocyte count but tremendous marrow nucleated red cell hyperplasia. There may be symptoms of anemia and perhaps slight splenic enlargement but no other significant physical findings are present. Red cells are mostly normocytic and normochromic but a few hypochromic microcytic cells may be seen. WBC and platelets may be slightly decreased. The bone marrow iron is greatly increased and tends to aggregate in siderotic granules in normoblasts and histiocytes. Radioiron studies have shown increased bone marrow red cell activity but decreased red cell release into the blood which indicates intramedullary hemolysis of the nucleated red cells.

There is no known treatment other than transfusions.

Dacie J V, & others. Refractory normoblastic anemia. *Brit J Haemat* 5 56 82 1959

**ANEMIA OF MYXEDEMA**

Some patients with very low thyroid function have a moderately severe anemia. A similar blood picture may be seen in hypopituitary disease. The RBC is rarely below 3 million/cu mm and the hemoglobin is rarely less than 9 Gm/100 ml. The anemia tends to be macrocytic and normochromic. However iron deficiency a frequent complication especially in women with menorrhagia will produce hypochromic microcytic anemia. Bone marrow cellularity is decreased with

increase in fat spaces. Nucleated red cells are normoblastic. White cells and platelets are normal.

Thyroid medication (see p 520) induces a gradual return to normal hemoglobin levels and RBC in 3-4 months.

Tudhope, J R. Anemia in hypothyroidism. *Quart J Med* 29 513, 1960

**HEMOLYTIC ANEMIAS****1. AUTOIMMUNE HEMOLYTIC ANEMIA****Essentials of Diagnosis**

- Fatigue malaise, pallor, jaundice
- Splenomegaly
- Persistent anemia and reticulocytosis
- Coombs test usually positive

Differentiate from iron deficiency anemia with relatively normal indices by means of the bone marrow hemosiderin stain and from pernicious anemia.

**General Considerations**

In acquired hemolytic anemia with auto-antibody (positive Coombs test) the red cells are coated with an abnormal protein. In this test well washed red cells are agglutinated by an antiserum developed against human serum or human globulin in rabbits or goats. The antibody is most active at 37°C (warm antibody). The red cell abnormality is usually nonspecific but rare blood group antibodies (e.g. anti-E or anti-e) are occasionally found. Normal donor cells given to patients with acquired hemolytic anemia have a shortened survival time. This type of hemolytic anemia develops during the course of about 30% of cases of chronic lymphatic leukemia, and accompanies or precedes some cases of Hodgkin's disease, macroglobulinemia, lupus erythematosus, and infectious mononucleosis. No specific etiology is found in about two thirds of cases.

Some patients have antibodies which are most active at 4°C (cold antibody). These are most commonly seen with viral pneumonia, sometimes secondary to lymphoma (especially reticulum cell sarcoma). In half of cases no underlying disease is found.

Acquired hemolytic anemia without antibody (negative Coombs test) is seen in some of



the above conditions, in uremia, cirrhosis, diffuse vasculitis, cancer, and some bacterial infections. In all of these disorders, normal donor cells have a shortened survival time.

### Clinical Findings.

**A. Symptoms and Signs:** Symptoms of anemia (weakness, pallor, dyspnea, palpitation, dizziness) or hemolysis (fever, jaundice, splenomegaly, hepatomegaly) may be present

**B. Laboratory Findings:** Acquired hemolytic anemia is usually normocytic and normochromic. Spherocytes and nucleated red cells may be seen. White cell and platelet counts are frequently elevated, but leukopenia and thrombocytopenia may occur. Reticulocytes are usually in excess of 10%, occasionally they are low. The bone marrow shows marked erythroid hyperplasia and ample hemosiderin. The Coombs test is usually positive. Indirect bilirubin may be elevated to 2 mg./100 ml. There is no bile in the urine. Stool urobilinogen may be greatly increased.

### Differential Diagnosis.

The hemoglobinopathies are differentiated by electrophoresis. In hemolytic anemia associated with cirrhosis the primary disease is evident. In hereditary spherocytosis and in congenital nonspherocytic hemolytic anemia the Coombs test is negative. In a recently recognized condition, refractory normoblastic anemia with intramedullary hemolysis, the reticulocyte count is low, bone marrow very hyperplastic with many siderocytes (erythrocytes containing nonhematin iron), and donor blood survives normally.

### Complications.

The hemolytic anemia may become acute, with shock, upper abdominal pain, and prostration. Thrombocytopenic purpura may develop. Gallstones may form.

### Treatment.

Treatment must often be directed against the underlying disease. Transfusions are only palliative, and their effects are dissipated rapidly since donor cells are also destroyed at an accelerated rate. There is no specific medication.

**A. Medical Treatment:** Prednisolone (or equivalent), 10-20 mg. 4 times daily, is given orally until normal hemoglobin values are reached or undesirable side effects develop. The daily dose is decreased by 5 mg. each week until the smallest dose needed to maintain normal hemoglobin levels is being given.

Occasionally, medication can then be discontinued. Patients must be reexamined every 4 weeks even when in remission because there is always a danger of sudden relapse.

**B. Surgical Treatment:** When steroids fail or when large doses are required for maintenance, splenectomy must be considered. Preliminary  $Cr^{51}$  red cell life span determinations and body surface counting over the spleen to determine splenic radioactivity are essential before the decision to operate is made. Only when splenic radioactivity is more than twice normal, as compared to the liver, is splenectomy likely to be of value.

### Prognosis.

In idiopathic acquired hemolytic anemia, prolonged remissions may occur spontaneously or following splenectomy or corticosteroid therapy, some cases are fatal. Often the prognosis depends upon that of the underlying disorder.

Dacie, J. V.: The auto-immune hemolytic anemias. *Am. J. Med.* 18, 810-21, 1955.

## 2. HEREDITARY SPHEROCYTOSIS (Congenital Hemolytic Anemia; Congenital Hemolytic Jaundice)

### Essentials of Diagnosis.

- Malaise, abdominal discomfort.
- Jaundice, anemia, splenomegaly.
- Spherocytosis, increased osmotic fragility of red cells, negative Coombs test.

In acquired hemolytic anemia the Coombs test is positive and a hereditary incidence is lacking. In congenital nonspherocytic hemolytic anemia the osmotic fragility is normal. Jaundice may suggest biliary tract disease or congenital hyperbilirubinemia, osmotic fragility and red cell survival tests should be done. The large spleen associated with anemia may suggest leukemia; proper examination of blood and bone marrow will rule out that disease.

### General Considerations.

In hereditary spherocytosis the red cells are abnormally susceptible to glucose deprivation; they are thick and relatively inelastic, they become "stuck" in the spleen and are

destroyed. When red cells from a patient with hereditary spherocytosis are transfused to a normal recipient they are also destroyed in the (normal) spleen. On the other hand normal donor blood survives normally in a patient with hereditary spherocytosis. The disease is chronic hereditary transmitted by a dominant gene and is seen in all races (rarely in Negroes). It may be first manifested in the newborn period and may resemble hemolytic disease due to ABO incompatibility but in some patients the disease is not discovered until after the age of 70.

### Clinical Findings

**A Symptoms and Signs** There may be easy fatigability and moderate and constant jaundice. The spleen is always enlarged and may cause left upper quadrant fullness and discomfort. Splenic infarction may cause acute pain. The anemia may be intensified during infections following trauma and during pregnancy.

On rare occasions an acute aplastic anemia develops with profound anemia and in some cases fever, headache, abdominal pain and pancytopenia with hyposplenic marrow. In occasional instances there may be no clinical findings; the diagnosis is made only because the discovery of the disease in a more severely afflicted relative has led to an intensive search and laboratory testing of the blood.

**B Laboratory Findings** The RBC is moderately decreased (3-4 million/cu mm). The red cells are small (MCV 70-80 cu  $\mu$ ) and hyperchromic (MCHC = 38-40%). Spherocytes in varying numbers are seen on the smear. The reticulocyte count is usually increased. The white cell and platelet counts are only moderately increased.

In the bone marrow there is marked erythroid hyperplasia. Hemosiderin is present in only moderate amounts since the spleen is the main reservoir of iron in this disorder.

The osmotic fragility of the erythrocytes is increased, particularly after incubation for 24 hours at 37°C (99°F). Autohemolysis of blood incubated for 48 hours is greatly increased. Incubation with glucose tends to reverse these abnormalities. Serum bilirubin and stool urobilinogen are usually elevated. The Coombs test is negative.

### Complications

Gallstones composed principally of bile pigments (reflecting increased metabolism of hemoglobin) occur in up to 85% of adults and may develop even in children. Leg ulcers are

occasionally seen. During febrile illnesses aplastic crises may occur with profound anemia and decreased WBC and platelets but little jaundice.

### Treatment

There is no specific medical treatment for this disorder.

**A Surgical Treatment** Splenectomy is indicated in all cases once the diagnosis is definitely established, even if the anemia is minimal and there is no jaundice. Preoperative transfusion is rarely necessary. When there is associated cholelithiasis, splenectomy should precede cholecystectomy unless both procedures are done at the same time. Splenectomy is usually deferred until after the first few years of life.

**B Treatment of Hemolytic Crisis** Prompt and adequate transfusion therapy is necessary to prevent cardiovascular collapse. Antibiotics may be necessary to treat precipitating infections.

### Prognosis

Splenectomy eliminates anemia and jaundice in over 90% of cases but abnormal red cell morphology and abnormal osmotic fragility persist. Red cell life span is normal after splenectomy.

Young L E Hereditary spherocytosis  
Am J Med 18:486-97 1955

## 3. ACUTE HEMOLYTIC ANEMIA

### Essentials of Diagnosis

- Sudden onset with chills, fever, nausea, vomiting, or pain in abdomen or back.
- Pallor, slight jaundice, splenomegaly.
- Red or black urine.

The fulminating onset of acute hemolytic anemia with chills and fever may simulate an infection. The abdominal pain may suggest surgical illness. The profound anemia suggests blood loss. In acute hemolytic anemia, however, the serum is invariably pigmented as a result of the products of hemolysis. A pink serum indicates free hemoglobin; a brown serum, methemalbumin; and a yellow serum, bilirubin.

### General Considerations.

Acute hemolytic anemia may be drug-induced, especially in sensitive individuals (see Primaquine-sensitive hemolytic anemia, p. 272); it may be due to certain infections, e.g., *Escherichia coli* infections, hemolytic streptococcal septicemia, *Clostridium welchii* infections, malaria; it may be seen in some forms of cancer and malignant lymphomas, and in some diseases of uncertain origin, e.g., lupus erythematosus and infectious mononucleosis. It is usually seen during the course of paroxysmal nocturnal hemoglobinuria (see below), thrombotic thrombocytopenic purpura (see below), paroxysmal cold hemoglobinuria, and when high titered cold agglutinins develop during convalescence from viral pneumonia. Sometimes the cause is not known.

### Clinical Findings.

**A. Symptoms and Signs:** The disease has a fulminating onset with chills, fever, abdominal pain, pallor, and often jaundice. Weakness and tachycardia may be present also.

**B. Laboratory Findings.** The anemia is normocytic and normochromic. Spherocytes, burr cells, microspherocytes, and nucleated red cells may be seen. The WBC may reach 50,000/cu. mm. and the platelet count 1 million/cu. mm., but occasionally both are decreased. A blood smear stained with methyl violet may show small granules (Heinz bodies), which are not visible with Wright's stain. Reticulocytes may be greatly increased. The Coombs test is usually negative.

The bone marrow is hyperplastic, with a predominance of nucleated red cells. There may be hemoglobinemia lasting a few hours, followed by methemalbuminemia (manifested by a brown discoloration of the serum) for a few days and usually a moderately elevated indirect bilirubin value. Haptoglobins disappear from the plasma. Haptoglobin, a glycoprotein migrating electrophoretically with  $\alpha_2$  globulin, can normally bind up to 200 mg./100 ml. of free hemoglobin, it disappears in most hemolytic anemias.

The urine may contain hemoglobin and hemosiderin and urobilinogen may be elevated, but there is no bile. Stool urobilinogen is increased. Red cell enzyme studies may show a deficiency of glucose-6-phosphate dehydrogenase, cold agglutinins may be found in atypical pneumonia, slightly acid serum may hemolyze the cells in paroxysmal nocturnal hemoglobinuria (Ham's test); and a circulating hemolysin may be found in paroxysmal cold hemoglobinuria (Donath-Landsteiner test).

### Complications.

Shock may occur if the decrease in circulating red cell mass is sufficiently abrupt or severe. Acute tubular necrosis secondary to profound ischemia may develop and may lead to acute renal failure.

### Treatment.

Acute hemolytic anemia may be a medical emergency. The patient should be hospitalized, all medications discontinued, and possible causes investigated.

Spontaneous remission frequently occurs. Even patients who are not critically ill are observed for a few days for a gradual decline of reticulocytosis, followed by a hemoglobin rise of 1-2 Gm./100 ml./week. Under these circumstances only supportive therapy need be given.

**A. General Measures:** Since acute renal failure is a potential hazard, serum electrolytes and BUN are determined and strict attention is paid to fluid intake and output and electrolyte administration.

**B. Transfusions:** Transfusions are used only to combat shock or anoxia, packed red cells are preferable to whole blood. Rarely is it necessary or desirable to raise the hemoglobin level above 8 Gm./100 ml. with transfusions.

**C. Corticosteroids:** If reticulocytosis persists and hemoglobin levels do not rise, if there is a continuous drop in hemoglobin, or if the patient is severely ill, give prednisolone (or equivalent), 10-20 mg. 4 times daily. Steroids are continued until serum and urine are clear of hemolytic products and the hemoglobin level is normal. The daily dose is decreased by 5 mg. each week. Splenectomy is rarely if ever indicated in acute hemolytic anemia.

### Prognosis.

Acute hemolytic anemia usually remits spontaneously, either because the offending agent is removed or because only a portion of the patient's red cells, usually the older ones, are sensitive to the toxin. Hemolytic anemias secondary to serious underlying disorders such as metastatic cancer, thrombotic thrombocytopenic purpura, or *Clostridium welchii* infection (as seen with induced abortion) are often rapidly fatal.

Dacie, J. V.: The auto-immune haemolytic anemias. *Am. J. Med.* 18:810-21, 1955.

#### 4 PRIMAQUINE SENSITIVE HEMOLYTIC ANEMIA (And Anemias Due to Other Drug Sensitivities)

This is a drug-induced acute hemolytic anemia which occurs in persons of particular racial groups who have genetically transmitted errors of metabolism. The most important defect is thought to be a deficiency of glucose 6 phosphate dehydrogenase in the erythrocytes and, to a variable degree, in other tissues. There is also a deficiency in the reduced form of catalase and glutathione. The trait is sex linked and of intermediate dominance. It finds its full expression in males and homozygous females and intermediate expression in heterozygous females. Ten to 15% of American Negro males and 1-2% of American Negro females have this disorder.

When not challenged by a drug, the RBC, red cell indices, and red cell morphology are entirely normal although the red cell survival time is slightly shortened. More than 40 drugs and other substances are capable of inducing hemolysis, including antimalarials sulfonamides, e.g., salicylazosulfapyridine (Azulfidine<sup>®</sup>), sulfamethoxypyridazine (Kynex<sup>®</sup>), sulfisoxazole (Gantrisin<sup>®</sup>), nitrofurans, and pyretics, analgesics, sulfones, water soluble vitamin B, and uncooked fava beans. Favism occurs principally in the Mediterranean area and is most common in Sardinia.

Several laboratory methods have been devised for identifying susceptible individuals. There is a glutathione stability test, a dye reduction test using cresyl blue, and a methemoglobin reduction test.

Management consists of withdrawal of the drug or toxic substance. Recovery is the rule.

Davies, P. Favism, a family study. *Quart J Med* 31: 157-75, 1962.

Tarlov, A. R., & others. Primaquine sensitivity. *Arch Int Med* 109: 209-34, 1962.

#### 5 PYRIDOXINE-RESPONSIVE ANEMIA

This is a very rare moderate to severe anemia characterized morphologically by hypochromia and microcytosis accompanied by hyperferrremia and hemosiderosis of the reticuloendothelial tissues. Hemoglobin may be restored to normal by large doses (50-200 mg 1 M daily) of pyridoxine, but the microcytosis and hypochromia persist. It must be distin-

guished from the so-called sideroachrestic anemias, iron deficiency anemia, and Cooley's anemia. Impaired heme production and faulty globin synthesis appear to be involved. Ferrokinetic measurements indicate that the red cells have shortened life spans and that there is ineffective erythropoiesis. This anemia is not associated with the other signs of pyridoxine deficiency such as CNS and skin manifestations.

Raab, S. O., & others. Pyridoxine-responsive anemia. *Blood* 18: 285-302, 1961.

#### 6. ANEMIA OF LEAD POISONING

Lead poisoning in the adult may produce a mild anemia. There may be slight pallor but no jaundice and the spleen is not enlarged. The red cells are normocytic, slightly hypochromic and may show coarse or fine stippling. Reticulocytes are slightly elevated. The white cells and platelets are normal. The bone marrow shows normal activity. Red cell Cr<sup>51</sup> survival shows moderately diminished red cell life span (half life 18-28 days). The osmotic fragility is decreased. Urine coproporphyrin is greatly increased. After treatment with a chelating agent, there is a five- to ten-fold increase of coproporphyrin and lead in the urine.

Lead interferes with hemoglobin synthesis at several levels. It inhibits heme synthesis and prevents the proper utilization and incorporation of iron into protoporphyrin. It especially inhibits globin synthesis. As a result the following substances accumulate in the urine of patients with lead poisoning: delta aminolevulinic acid, porphobilinogen, coproporphyrin, and lead.

Byers, R. K. Lead poisoning. Review of the literature and report on 45 cases. *Pediatrics* 23: 585-603, 1959.

#### 7. HEMOLYTIC TRANSFUSION REACTIONS

##### Essentials of Diagnosis

- Chills and fever during blood transfusion
- Pain in the back, chest or abdomen
- Hemoglobinemia and hemoglobinuria

In all significant hemolytic transfusion reactions there is immediate,

grossly visible hemoglobinemia. A normal serum color during or immediately after a transfusion rules out hemolysis as the cause of even severe symptoms, and other causes (e.g., leuco-agglutinins or allergy) must be considered.

#### General Considerations.

In transfusion reaction due to ABO incompatibility the donor cells are hemolyzed instantaneously in the general circulation. In reactions due to incompatibility in some of the other blood groups (such as Rh), hemolysis is more gradual and may last hours, most of the destruction occurring in the reticuloendothelial tissues.

Serious transfusion reactions are often caused by clerical errors such as improper labeling of specimens or improper identification of patients.

Incompatibility due to the less common blood group antibodies may be detected only by a Coombs test.

#### Clinical Findings.

**A. Symptoms and Signs:** There may be chills and fever, and pain in the vein at the local injection site or in the back, chest, or abdomen. Anxiety, apprehension, and headache are common. In the anesthetized patient, spontaneous bleeding from different areas may be the only sign of a transfusion reaction.

**B. Laboratory Findings:** Post-transfusion blood counts fail to show the anticipated rise in hemoglobin, spherocytes may be present on the blood smear, and initial leukopenia at 1-2 hours is followed by a slight leukocytosis. Free hemoglobin can be detected within a few minutes. Methemalbumin, an acid hematin-albumin complex giving a brown color to the serum, may appear after a few hours and persist for several days. Elevated bilirubin levels, when present, are usually greatest 3-6 hours after the transfusion. Haptoglobin disappears from the serum. Hemoglobinuria and oliguria may occur.

After the reaction occurs it is essential to draw a fresh specimen from the patient, perform a direct Coombs test, and to check it against the blood in the transfusion bottle (not the pilot tube) by the indirect Coombs test. If the indirect Coombs test is positive, exact identification of the offending antibody may be made by matching the patient's serum against a panel of known test cells. Unusual antibodies found in transfusion reactions are, in order of frequency, anti-c, anti-K (Kell), anti-E, anti-Fy<sup>a</sup> (Duffy), anti-Le<sup>a</sup> (Lewis), anti-Jk<sup>a</sup> (Kidd), and anti-C.

#### Differential Diagnosis.

Transfusion in the presence of leuco-agglutinins, which usually develop after 5 or more transfusions or after previous pregnancy, may cause severe chills and high fever. There is no fall in hematocrit, a cross-match is compatible, there are no pigmentary changes in the serum, and leuco-agglutinins can be demonstrated *in vitro* when the patient's serum is matched against several white cell donors. In allergic transfusion reactions, the above tests also are negative and no leuco-agglutinins are present.

#### Complications.

Acute tubular necrosis and azotemia may follow a severe transfusion reaction.

#### Treatment.

Hives, chills, and fever following the transfusion of blood are not necessarily due to hemolysis. If the patient's serum remains clear, the transfusion may be continued. However, once the diagnosis of hemolysis is well established by appropriate tests the main problems are to combat shock and treat possible renal damage.

**A. Treatment of Shock:** After antibody screening of the patient's serum, transfusions with properly matched blood may be advisable. If no satisfactory answer can be found to the reason for the transfusion reaction, plasma expanders, such as dextran, and plasma may have to be used instead of whole blood. Pressor agents may be necessary.

**B. Treatment of Kidney Disease:** Measure the urine output every hour. If oliguria occurs, treat as for acute renal failure (see p. 741). No attempt should be made to alkalize the urine by giving sodium bicarbonate or I.V. sodium lactate or to give large volumes of fluid to force diuresis.

#### Prognosis.

The hemolysis is self-limited. Renal involvement is comparatively infrequent. The death rate from hemolytic transfusion reactions is about 10%.

Davidsohn, I., & K. Stern: Blood transfusion reactions: their causes and identification. *M. Clin. North America* 44:281-92, 1960.

## 8 OVALOCYTOSIS (Hereditary Elliptocytosis)

Ovalocytosis is inherited as a dominant trait and is equally common in males and females. The determining gene is on the same chromosome that carries the Rh blood group gene. Twenty five to 90% of the red cells may be oval.

The disorder is usually asymptomatic. Anemia is usually not present and the red cell indices are normal. Some patients have moderate anemia, increased reticulocyte counts and serum bilirubin and moderately shortened red cell survival times. In these patients the spleen may be enlarged and splenectomy may be of benefit.

Motulsky A G & others. The lifespan of the elliptocyte. Blood 8 57 77 1954

## 8 PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Paroxysmal nocturnal hemoglobinuria is a chronic hemolytic anemia of variable severity characterized by rather constant hemoglobinemia and hemosiderinuria and recurrent episodes of acute hemolysis with chills, fever, pain and hemoglobinuria.

The basic disorder is an unknown intracellular defect. Hemolysis is produced by interaction between the abnormal cells and several factors present in normal serum: magnesium, properdin and the complement like components.

The onset is usually in adult life; there is no familial tendency. There may be some enlargement of the spleen and liver. Red cell white cell and platelet counts are decreased and the reticulocyte count is increased. The bone marrow is usually hyperactive but may be hypoplastic.

Iron deficiency anemia may be present also as demonstrated by the absence of bone marrow hemosiderin. The indirect serum bilirubin is elevated. Hemoglobinemia and methemalbuminemia are often present. Haptoglobins are absent and red cell acetylcholinesterase level is low. The intrinsic red cell defect is demonstrated by finding hemolysis on incubation of the patient's red cells in normal acidified serum (Ham's test). Hemoglobin electrophoresis, osmotic fragility and the Coombs test are normal.

Complications consist of overwhelming infection, aplastic crises and thromboses.

Transfusion reactions occur when the donor blood (plasma) hemolyzes the patient's red cells.

Washed red cell transfusions are given for severe anemia or complications such as trauma, infections, thromboses or leg ulcers. The administration of 1 L of 6% dextran solution, preferably of relatively high molecular weight (150,000) before transfusion may prevent hemolysis of the patient's own cells by donor serum.

Crosby W H. Paroxysmal nocturnal hemoglobinuria. Relation of the clinical manifestations to underlying pathogenic mechanisms. Blood 8 768 812 1953

Differential Diagnosis of Paroxysmal Hemoglobinuria

	Attacks Precipitated By	Site of Pain	Plasma Discoloration	Anemia	Urinary Pigment	Specific Test
Paroxysmal nocturnal hemoglobinuria	Sleep	Lumbar abdominal legs shoulder girdle	Prominent	Chronic	Hemoglobin	Ham and Crosby tests
Cold hemoglobinuria	Cold	Abdominal cramps backache	Prominent	During attacks only	Hemoglobin	Serologic test for syphilis Donath Landsteiner
March hemoglobinuria	Exercise	Lumbar	Prominent	None	Hemoglobin	Provocative exercise test
Idiopathic myoglobinuria	Usually exercise	Muscles	None	None	Myoglobin	Spectroscopic examination of myoglobin

## 10. HEREDITARY NONSPHEROCYTIC HEMOLYTIC ANEMIA

### Essentials of Diagnosis.

- Moderate anemia.
- Familial and congenital.
- Spleen slightly enlarged.
- No spherocytes, osmotic fragility normal.
- High reticulocyte count.

In hereditary spherocytosis the red cells are small and round, osmotic fragility is increased, and jaundice is often prominent

### General Considerations.

This is a heterogeneous group of hemolytic anemias caused by intrinsic red cell defects. The onset is in childhood, many of these disorders are inherited as a mendelian dominant trait. All races are affected, but northern Europeans more so than others. There may be an enzyme defect in the Embden-Meyerhoff pathway (pyruvate kinase deficiency) or an abnormality in the hexosemonophosphate shunt (glucose-6-phosphate dehydrogenase). In other cases no enzyme defect has been demonstrated. Two types of hereditary nonspherocytic hemolytic anemia are recognized type I, with normal autohemolysis, and type II, with greatly increased (20-50%) autohemolysis at 48 hours.

### Clinical Findings.

**A. Symptoms and Signs** Severe anemia may be fatal in infancy. The disorder is usually recognized in childhood. There may be symptoms of anemia, slight jaundice, and a palpable spleen.

**D. Laboratory Findings** The red cells may be normal or slightly enlarged. Howell-Jolly bodies and Pappenheimer bodies (iron particle inclusions visible with Wright's stain) and stippling may be prominent, especially after splenectomy. The reticulocyte count is greatly elevated even if the anemia is only mild. White cell and platelet counts are normal. The marrow shows tremendous erythroid hyperplasia and normal hemosiderin. Osmotic fragility and hemoglobin electrophoresis are normal.

### Differential Diagnosis.

In acquired hemolytic anemia the Coombs test is positive. In refractory normoblastic anemia the reticulocyte count is low and the spleen is not palpable. In the hemoglobinopathies the diagnosis is made by hemoglobin electrophoresis.

In the newborn this condition may be very difficult to differentiate from hemolytic anemia due to ABO incompatibility.

### Complications.

There may be associated cholelithiasis and cholecystitis.

### Treatment.

Transfusions may be necessary. Splenectomy is of no benefit

De Gruchy, G C., & others Non-spherocytic congenital hemolytic anemia. Blood 16: 1371-97, 1960

## ABNORMAL HEMOGLOBINS

The human red cell contains 200-300 million molecules of hemoglobin. Each molecule contains 4 heme groups and one globin molecule. The globin molecule is composed of 2 pairs of polypeptide chains. One pair has been designated arbitrarily as the alpha chain and the other the beta chain on the basis of many differences involving long amino acid sequences. The members of each pair are identical. Each chain is made up of 28 peptides. The production of alpha and beta chains is under the control of 2 different genetic loci, which are independent (that is, not closely linked).

Three different types of hemoglobin are normally present, 97% is hemoglobin A. The other 2 normal hemoglobins are present in trace amounts of 1-3%. Hemoglobin A<sub>2</sub> possesses an alpha chain but, in place of the beta chain, a pair of delta polypeptides which differ from the beta chain probably in less than 10 amino acids. Fetal hemoglobin (hemoglobin F) contains a gamma chain instead of a beta chain and differs from the latter in numerous amino acid substitutions. Beta, delta, and gamma chains seem to be the result of closely linked alleles.

Hemoglobinopathies involve abnormalities in the hemoglobin chains. These are due to changes in the DNA template (a different order of bases in the one locus resulting in the production of different amino acids - and therefore faulty protein) Differences between normal and abnormal hemoglobins are relatively minute. For instance, sickle (S) hemoglobin differs from normal hemoglobin in the single amino acid of peptide No. 4 of the beta chain, i.e., one out of 300 amino acids. Yet this

## Hematologic Findings in Hemoglobinopathies \*

Hemoglobin Disorder	Erythrocytes (mill / cu mm)	Hemoglobin (Gm / 100 ml)	MCV (cu $\mu$ )	MCHC (%)	Reticulocytes (%)	Target Cells (%)	Hemoglobins (%)	Fetal Hemoglobins (%)
Normal (adult men and women A/A)	4 2-6 2	12 18	82-82	32 36	0 5-1 5	0	2-3 (A <sub>2</sub> )	0.2
A/S	N	N	N	N	N	0	22-48 (S)	0 trace
S/S	1 5 4 0	2 11	72-100	30 36	5 30	Some	80-100 (S)	0 20
S/Thalassemia	2 0 5 0	6 14	65 90	25 35	4 20	Many *	22-80 (S)	0 17
S/C	2 5 5 5	8 1 15 1	65 80	28 34	0 2-10	5 85	[37-67 (C)] [30-60 (S)]	0 8
S/D	2 5 4 0	7 12	100 118	30-32	7-13	2 Some	[7-50 (S)] [7-50 (D)]	Trace
S/E	4 8 5 6	11 4 13 2	83 95	25	...	Some	[40 (E)] [80 (S)]	?
A/C	N	N	N	N	N	0 40	25 39 (C)	0
C/C	3 1 5 0	7 14 5	55 83	23 38	1 12	20-100	87-100 (C)	0 4
C/Thalassemia	4 6 5 4	4 1-12 7	50 67	22 35	2-7	20 80	29-83 (C)	Trace 3
A/D	N	N	N	N	1-2 8	0	< 50 (D)	0
D/D	5 5-7 1	12 13	83 87	28 35	1 1 5	50 80	100 (D)	0
A/E	N	N	N	N	N	Few	20-50 (E)	0
E/E	4 0 8 4	8 8 18 3	51-76	27 35	0-4 2	9 78	94 100 (E)	Trace 6
E/Thalassemia	1 3-4 2	2 3 8 5	61-83	24 32	1-9 5	4-44	15-45 (E)	55 85
H/Thalassemia	1 6 6 4	2 7 11 3	49 113	17 30	2 22	1 30	35 40 (H)	Trace 4
Thalassemia minor	4 7 5	8 3 13 2	51 80	25 31	0 5 9 0	0 10	1-8% A <sub>2</sub>	0 10
Thalassemia major	1 4 0	2-8	60 80	17 30	1 5-38	0-50	2-3 A <sub>2</sub>	10-90
Hereditary persistence of fetal hemoglobin	N	N	N	N	N	0	0	10 30

\*Modified from J V Dacie The Hemolytic Anemias Congenital and Acquired, 2nd Edition  
Part 1 Grune & Stratton 1960



small difference has far-reaching clinical effects which produce sickle cell disease. Most of the well-known hemoglobinopathies involve abnormalities of the beta chains. A few alpha chain abnormalities are known.

Although in thalassemia no hemoglobin of abnormal electrophoretic mobility has as yet been demonstrated, there may be a structural abnormality of either the alpha or beta chain, which in some way controls the rate of normal hemoglobin synthesis. There is evidence that not all thalassemias are alike. Some forms act as if they were allelic to the common hemoglobinopathies, e.g., those involving hemoglobins S or C. In other families thalassemia appears to be inherited independently of S or C, which implies an abnormality of the alpha chain.

Jensen, W.N.: *The Hemoglobinopathies*. Disease-A-Month, Year Book, Feb. 1961.

## 1. HEREDITARY HEMOGLOBINOPATHIES

Certain hereditary hemolytic anemias seen almost exclusively in Negroes are characterized by the genetically determined presence of an abnormal type of hemoglobin in the red cells.

The heterozygous hemoglobin trait syndromes usually represent asymptomatic carriers, e.g., in sickle cell trait, which occurs in about 8% of American Negroes, there is no anemia. With hemoglobin C trait, which occurs in about 3% of American Negroes, there is no anemia but target cells are common.

The homozygous hemoglobin disorders are usually severe. The most common and in general the most severe is sickle cell anemia (homozygous S disease). Homozygous C disease is much less serious and much rarer.

Double heterozygous diseases, e.g., combination hemoglobin S and C disease (less severe than classical sickle cell anemia) may occur. Other double heterozygous forms between S and C and thalassemia may occur, but anemia is mild or moderate.

In general, all of the homozygous disorders with the exception of sickle cell anemia - and all of the double heterozygous disorders - are characterized by splenomegaly.

Fetal hemoglobin is increased in double heterozygous disorders when one of the genes is a thalassemia gene. Some fetal hemoglobin is also present in sickle cell anemia.

The table on p. 276 lists some of the more common hemoglobinopathies.

Chernoff, A.I.: Some genetic considerations of the abnormal hemoglobin in light of their amino acid structure. *Angiology* 13:151-70, 1961.

Jensen, W.N.: *The hemoglobinopathies*. Disease-A-Month, Year Book, 1961.

## 2. SICKLE CELL ANEMIA

### Essentials of Diagnosis.

- Recurrent attacks of fever, and pain in the arms, legs, or abdomen since early childhood in a Negro patient.
- Anemia, jaundice, reticulocytosis, positive sickle cell test, and demonstration of abnormal (S) hemoglobin.

The spleen is not enlarged in adult sickle cell anemia. An anemic Negro patient with an enlarged spleen and a positive sickle cell preparation probably has a double heterozygous disorder instead (e.g., "sickle thalassemia" rather than sickle cell anemia). The sickle cell test does not reliably differentiate between sickle cell anemia (the homozygous disorder) and sickle cell trait (the heterozygous carrier state). In sickle cell anemia the RBC is always low, the finding of a low hemoglobin with a normal RBC in a Negro patient with a positive sickle cell preparation is not compatible with sickle cell anemia but suggests iron deficiency anemia plus sickle cell trait.

### General Considerations.

Sickling of the chemically abnormal hemoglobin occurs at low oxygen tension, especially at a low pH. The S (sickle) hemoglobin is less soluble in deoxygenated (reduced) form, the viscosity of the whole blood consequently increases, and the result is stasis and the formation of painful sickle cell thrombi with increased mechanical fragility of the red cells and hemolysis. These physical changes of the red cells are largely responsible for the clinical findings and the anemia.

Sickle cell anemia is a hereditary disorder, essentially confined to Negroes; the abnormal hemoglobin is transmitted as a single dominant gene. Heterozygous carriers have mixtures of normal and sickle hemoglobin in all of their red blood cells.

### Clinical Findings.

A. Symptoms and Signs: The diagnosis is usually made in childhood, but occasionally a

patient will reach adult life before a well documented crisis develops. Patients with sickle cell anemia tend to be of asthenic build with long spindly legs. Constant scleral icterus of moderate degree is common. The crisis consists of attacks of bone and joint pain or abdominal pain, sometimes with fever, lasting hours or days. The tender, rigid abdomen may resemble surgical illness and may last for hours or days. Cerebral thrombosis may occur, producing headaches, paralysis, and convulsions.

**B. Laboratory Findings** Anemia is moderately severe (RBC is usually 1.5-2.5 million/cu. mm.), normocytic and normochromic. Some sickle cells are usually present on the blood smear. Reticulocytes may be 15-20%. When a drop of fresh 2% solution of sodium metabisulfite is mixed on a slide with a drop of blood, sickling of most of the red cells occurs in a few minutes. A WBC of 20-30 thousand is not unusual, and there may be as many as 100 nucleated red cells per 100 white cells. The blood values may remain constant even during a clinical crisis. The bone marrow shows marked erythroid hyperplasia, with more nucleated red cells than white cells. Hemosiderin is present in ample amounts. The indirect bilirubin may be elevated to 2 mg/100 ml., and there may be a slight elevation of the plasma hemoglobin. The specific gravity of the urine is relatively fixed at 1.010, and there may be hemosiderinuria. X-rays of the bones may show varying degrees of cortical thinning, diffuse osteoporosis, and thickening of the trabecular markings.

#### Differential Diagnosis.

Sickle cell anemia is differentiated from other hemoglobinopathies by hemoglobin electrophoresis, the sickle cell test, and fetal hemoglobin determination. Hematuria may simulate genitourinary tumor, tuberculosis, or vascular disease. Bone and joint pain may resemble rheumatic fever. The abdominal pain may simulate surgical abdominal conditions, persistence of normal bowel sounds in sickle cell crisis may be a helpful differential diagnostic finding.

An electrophoretic pattern indistinguishable from that of sickle cell anemia may be found in the following. (1) Sickle cell-hemoglobin D disease: Hemoglobin D has the same electrophoretic mobility as hemoglobin S, but electrophoresis on agar gel at pH 6.0 differentiates these 2 hemoglobins. (2) Some instances of sickle-thalassemia. Hemoglobin A sometimes cannot be detected by electrophoresis in sickle-thalassemia because its

formation is suppressed by the thalassemia gene. Family studies may distinguish sickle-thalassemia from sickle cell anemia. (3) Sickle cell-persistent fetal hemoglobin syndrome (see p. 279).

#### Complications.

Complications include leg ulcers, bone infarction, aseptic necrosis of the femoral head, osteomyelitis (especially due to *Salmonella*), cardiac enlargement with auscultatory findings similar to those of mitral stenosis, recurrent gross hematuria, and cholelithiasis. Following infection there may be an aplastic crisis.

#### Treatment.

Treatment is symptomatic. There is considerable variation in the frequency and severity of clinical manifestations.

**A. Treatment of Clinical Crisis:** Place the patient at bed rest and give analgesics. Local measures, cobalt, nasal oxygen, carbonic anhydrase inhibitors, and vasodilators have been employed with little success. Sodium bicarbonate, 3.5 mEq./Kg./hour I.V., or plasma expanders (e.g., dextran), plasma, and glucose solution with 0.45% sodium chloride solution have been said to be occasionally successful in relieving pain.

**B. Treatment of Hemolytic and Aplastic Crisis:** Transfusions are mandatory. The hemoglobin level should be raised to 12-14 Gm/100 ml. Adequate hydration is necessary. A careful search for infections should be made and appropriate antibiotic therapy instituted.

#### C. Treatment of Complications

1. Leg ulcers - The legs are immobilized and elevated under a heat cradle. The ulcer area is cleansed and debrided. The patient is given sufficient blood to raise the hemoglobin level to 12-14 Gm./100 ml.
2. Cholelithiasis or orthopedic disorders requiring surgery - Give sufficient preoperative blood to raise the hemoglobin level to 12-14 Gm./100 ml.
3. Sickle cell anemia appearing during pregnancy - Transfuse to 10-12 Gm./100 ml in the third trimester.
4. Pulmonary thrombosis and osteomyelitis are treated by standard methods.

#### Prognosis.

Many patients die in childhood of cerebral hemorrhage or shock. Others live beyond the age of 50 years. There is a tendency to progressive renal damage, and death from uremia may occur.

Individuals with sickle cell trait seldom develop clinical illness. Rare complications are gross hematuria, splenic infarction while flying in unpressurized aircraft, and pulmonary and visceral infarcts during illness associated with tissue hypoxia.

Singer, K.: The pathogenesis of sickle anemia. *Am. J. Clin. Path.* 21:858-65, 1951.

### 3. HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN

Patients with this disorder show no clinical or hematologic abnormalities, but their hemoglobin consists of 20-40% fetal hemoglobin together with hemoglobin A. The gene for persistent fetal hemoglobin is transmitted in a simple, mendelian manner, and appears to be allelic for hemoglobin S, hemoglobin C, or other beta chain hemoglobin abnormalities. No homozygous cases are known. The disorder is seen almost exclusively in Negroes. Patients who inherit the gene for hemoglobin S in addition to that resulting in persistence of hemoglobin F are indistinguishable on electrophoresis from patients with classic sickle cell anemia, but they have only minimal clinical manifestations.

Herman, E.C., & others: Hereditary persistence of fetal hemoglobin. *Am. J. Med* 29:9-17, 1960.

### 4. THALASSEMIA MINOR

#### Essentials of Diagnosis.

- Mild but persistent anemia.
- RBC normal or elevated
- Similar blood findings in one of the parents.
- Patient usually has a Mediterranean or southern Chinese racial background.

Thalassemia minor must be differentiated principally from iron deficiency anemia. It is not a severe anemia, the hemoglobin level is almost always above 9 Gm./100 ml., and serum iron, total iron-binding capacity, and marrow hemosiderin are normal.

#### General Considerations.

Thalassemia major (Cooley's anemia) represents the homozygous state of the thalas-

semia genes, whereas thalassemia minor represents the heterozygous form. It is probable that more than a single set of alleles is involved in thalassemia. This may account for the various clinical gradations between the major and minor forms of the disease. Thalassemia is both congenital and familial.

#### Clinical Findings.

**A. Symptoms and Signs:** There are usually no symptoms. The spleen may be slightly enlarged.

**B. Laboratory Findings:** The RBC may exceed 6 million/cu. mm. The hemoglobin does not fall below 9 Gm./100 ml. except during pregnancy. The red cells are very small (MCV = 50-70 cu.  $\mu$ ), and hemoglobin concentration often is only moderately reduced (MCHC = 29-31%). Target cells and stippled cells may be present. There is considerable variation in size and shape of the red cells - far greater than is noted in iron deficiency anemia of a comparable hemoglobin level. Some hypochromic macrocytes may be seen. Red cell patterns vary from one family to another. One group may have many target cells, another group may have many stippled cells. Reticulocytes vary from 1-9%, platelets and white cells are not remarkable.

The bone marrow shows increased numbers of nucleated red cells. White cells and megakaryocytes are normal. Hemosiderin is present. On starch block or cellulose acetate paper electrophoresis hemoglobin A<sub>2</sub> (a slow-moving component) is increased. Fetal hemoglobin is usually normal but may be slightly increased.

#### Differential Diagnosis.

Other hypochromic, microcytic anemias with normal or even increased serum iron and marrow hemosiderin are as follows:

**A. Certain hemoglobinopathies**, especially hemoglobin E disease and the so-called Lepore trait, are diagnosed by hemoglobin electrophoresis.

**B. Sideroachrestic anemia**, characterized by increased iron values, many sideroblasts, and biochemical evidence of disordered heme synthesis. Hemoglobin electrophoresis is normal.

**C. Pyridoxine-responsive anemia** (see p. 272).

**D. In lead poisoning** (see p. 272) and infections (see p. 282), the red cells may be hypochromic.

**Complications.**

Thalassemia does not respond to iron therapy, and unnecessary and prolonged treatment with parenteral iron could lead to excess iron storage.

**Treatment.**

No treatment is required, and unnecessary iron therapy must be avoided. During pregnancy, transfusions may be necessary to maintain hemoglobin above 8 Gm /100 ml.

**Prognosis.**

Patients with thalassemia minor have normal life spans.

Bannerman, R M. Thalassemia. Grune & Stratton, 1961.

**5. THALASSEMIA MAJOR**

(Cooley's Anemia, Mediterranean Anemia)

**Essentials of Diagnosis.**

- Severe anemia starting in early infancy
- Very large liver and spleen.
- Hypochromic, microcytic red cells with many erythroblasts
- Greatly elevated fetal hemoglobin

Other hemoglobinopathies involving varying mixtures of hemoglobin S, hemoglobin C, and others with thalassemia may give similar but less severe clinical pictures. Congenital nonspherocytic hemolytic anemia may resemble this disorder. Hemoglobin electrophoresis, determination of fetal hemoglobin, and family studies make the correct diagnosis.

**General Considerations.**

This is a hereditary disorder characterized by increased hemolysis due to an intracorpuscular defect involving abnormal hemoglobin synthesis and ineffective erythropoiesis. Two incomplete dominant abnormal alleles are present in this homozygous form of thalassemia; in thalassemia minor (the heterozygous form), only one such abnormal allele is present. The disease is found in patients of Mediterranean ancestry and from an area forming a wide band extending over northern Africa and southern Europe to Thailand and including Iran, Iraq, Indonesia, and southern China. Among the various peoples involved the incidence of thalassemia is up to 50% (usually about 5%).

**Clinical Findings.**

A. Symptoms and Signs: Severe anemia and a huge liver and spleen are usually recognized in early childhood. Jaundice is usually present.

B. Laboratory Findings: Severe microcytic, hypochromic anemia is present. Target cells and bizarre-shaped red cells are seen. Nucleated red cells are numerous. The reticulocyte count is moderately elevated. The platelet count and WBC are normal or increased. Serum bilirubin is elevated. Haptoglobins are absent. Paper hemoglobin electrophoresis is normal.  $A_2$  is not elevated, but fetal hemoglobin may be increased to 90%. The bone marrow shows tremendous erythroid hyperplasia and ample stainable iron.

C. X-ray Findings: Skeletal lesions (evident on x-ray) are most prominent in the skull and long bones and consist of increase of the medullary portion and thinning of the cortex, the so-called hair on end appearance.

**Treatment**

Regularly spaced transfusions are often necessary to maintain life. Rarely, folic acid may be helpful for associated folic acid deficiency. When secondary hemolytic anemia develops with evidence of accelerated splenic sequestration of transfused red cells, splenectomy may be helpful.

**Complications.**

There may be cardiorespiratory symptoms due to the chronic anemia. Leg ulcers and cholelithiasis may develop. Transfusion-induced iron overload, with myocardial hemosiderosis, may lead to cardiac arrhythmia. Intractable heart failure is a fairly common cause of death. Few patients survive into adult life.

Bannerman, R M. Thalassemia. Grune & Stratton, 1961.

**6 HEMOGLOBIN H DISEASE**

Hemoglobin H disease is a chronic microcytic anemia which is refractory to iron therapy. It is seen in Chinese and Filipinos and resembles thalassemia minor. The disorder is congenital and familial.

The spleen is enlarged, a moderate degree of anemia is present, and the reticulocyte count is elevated. Hemoglobin H differs from normal hemoglobin by its more rapid

electrophoretic mobility and by its instability. After incubation for 30 minutes at room temperature with 2% sodium metabisulfite, precipitates form in the red cells which are demonstrable by reticulocyte stain. Osmotic fragility is decreased, and red cell life span is shortened. The abnormal hemoglobin accounts for about a third of the patient's hemoglobin.

Rigas, D.A., & others: Hemoglobin H. J. Lab. & Clin. Med. 47:51-64, 1956.

## HYPERSPLENISM

### Essentials of Diagnosis.

- Large spleen.
- Pancytopenia.
- Active marrow.

Hypersplenism is characterized by "empty blood," "full marrow," and a big spleen. In leukemia and lymphoma the characteristic malignant cells are present in the blood, marrow, or lymph nodes.

### General Considerations.

The spleen may be enlarged because of a specific infiltrate, as in Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease, tuberculosis, or Bosch's sarcoma. Nonspecific enlargement may occur, as in rheumatoid arthritis (Felty's syndrome).

The most common form of hypersplenism is congestive splenomegaly, often due to portal hypertension secondary to cirrhosis. Other causes are thrombosis, stenosis, atresia, or angiomatous deformity of the portal or splenic vein, external pressure due to cysts, and aneurysm of the splenic artery.

In hypersplenism the platelet count, WBC, and to some extent the RBC are reduced because of sequestration by the enlarged spleen, there is very little evidence that the spleen exerts any depressant activity on the marrow.

### Clinical Findings.

A. Symptoms and Signs: Patients affected with hypersplenism due to congestive splenomegaly are usually under 35 years of age, the onset may be gradual, but there may be sudden hematemesis, gastrointestinal bleeding occurs in about half of cases.

The large spleen may cause abdominal fullness. There may be no symptoms, and the spleen is found accidentally during a routine examination. In other patients purpura may

be prominent or there may be hematemesis from esophageal varices. In primary splenic neutropenia there may be fever and pain over the splenic region.

B. Laboratory Findings: The anemia is often mild, normocytic and normochromic, and the reticulocyte count may be elevated. The  $Cr^{51}$  red cell life span is decreased, with evidence of increased splenic sequestration. Platelets and white cells, particularly the granulocytes, are greatly decreased, with a shift to the left.

The bone marrow shows varying degrees of generalized hyperactivity and many megakaryocytes.

### Differential Diagnosis.

Leukemia and lymphoma are diagnosed by marrow aspiration or lymph node biopsy and examination of the peripheral blood (WBC and differential). In hereditary spherocytosis there are spherocytes, osmotic fragility is increased, and platelets and white cells are normal. The hemoglobinopathies with splenomegaly are differentiated on the basis of hemoglobin electrophoresis. Thalassemia major becomes apparent in early childhood, and the blood smear morphology is characteristic. In myelofibrosis marrow biopsy shows proliferation of fibroblasts and replacement of normal elements. In idiopathic thrombocytopenic purpura the spleen is not enlarged.

### Complications.

Gastrointestinal hemorrhage due to bleeding from esophageal varices may be fatal. There may be bleeding due to thrombocytopenia.

### Treatment.

Therapy is usually that of the underlying condition. When the hematologic abnormalities are not severe, no treatment is required.

Splenectomy may be advisable for congestive splenomegaly due to a splenic vein abnormality alone and when hemolytic anemia or thrombocytopenic purpura are associated with the splenomegaly of tuberculosis, Gaucher's disease, or sarcoidosis.

If congestive splenomegaly is due to liver or portal vein disease, splenectomy should be done only in conjunction with a splenorenal, splenocaval, or portacaval shunt.

### Prognosis.

The prognosis is that of the underlying disorder. The course in congestive splenomegaly due to portal hypertension depends upon the degree of venous obstruction and

liver damage. If there is no hematemesis, the course may be chronic and relatively benign and splenectomy need not be done.

Combined Staff Clinic Hypersplenism Am  
J Med 11 494-506 1951

## SECONDARY ANEMIAS

Under this heading are listed several diseases frequently accompanied by moderate to severe anemia. The anemia is usually caused by a combination of shortened red cell life span and inadequate bone marrow compensation, so called relative bone marrow failure or sick cell syndrome. The red cells may be normal in appearance. The reticulocyte count may be slightly elevated. Platelets and white cells are normal. No abnormal serum factors are demonstrable. The bone marrow is active and erythropoiesis may be increased. Some of these disorders have their own characteristics which are described below. It is important to recognize complicating iron deficiency or folic acid deficiency, which can be treated specifically.

### 1. ANEMIA OF CIRRHOSIS

Some degree of anemia is almost invariably seen in the patient with cirrhosis.

(1) Iron deficiency due to blood loss may occur with gastritis, esophageal varices, hemorrhoids, or associated peptic ulcer.

(2) Folic acid deficiency and the characteristic megaloblastic picture is seen in 5% of cirrhotic patients with anemia.

(3) A moderately severe hemolytic anemia is seen most frequently. The red cells are thin, flat, macrocytic, and slightly hypochromic, and vary greatly in size but not in shape. Target cells are common, and the reticulocyte count is moderately elevated. The WBC is normal or elevated and the platelet count is usually increased. In some patients, particularly when the spleen is enlarged, white cell and platelet counts are decreased.  $Cr^{51}$  red cell survival studies show a half-life of 15-25 days. The Coombs test is negative. The bone marrow is hyperplastic and contains many erythroblasts, frequent plasma cells, and increased numbers of megakaryocytes. With acute exacerbation of chronic hepatitis, histiocytes filled with fat may be seen.

The hemolytic anemia of cirrhosis does not respond to any specific measures nor to corticosteroid therapy. The treatment is that of the underlying disorder.

Jandl, J H. The anemia of liver disease: observations on its mechanism. J Clin. Invest. 34 390-404, 1955.

### 2. ANEMIA OF CANCER

Anemia of cancer may be due to any of the following:

(1) Chronic blood loss with subsequent development of iron deficiency anemia.

(2) Hemolysis, usually moderate and demonstrable only by  $Cr^{51}$  red cell survival studies. Occasionally, hemolysis is severe and acute (see Acute hemolytic anemia, p 270).

(3) Replacement of functional marrow by the malignant tissue ('myelophthisic anemia').

Hyman, G A., & J L Harvey. The pathogenesis of anemia in patients with carcinoma. Am J Med 19 350-6, 1955.

### 3. ANEMIA OF INFECTION

Anemia usually develops only in chronic infections which are clinically obvious, e.g., in patients with lung abscess, empyema, pelvic inflammatory disease, tuberculosis, or rheumatoid arthritis. The anemia in these cases is only moderately severe, and the hemoglobin rarely falls below 9 Gm/100 ml. The cells are normocytic and may be slightly hypochromic. The reticulocyte count is normal, low, or slightly elevated. Platelets and white cells are not remarkable, although there may be toxic granulation of polymorphonuclear cells. The serum iron is low, but (in contrast to iron deficiency anemia) the total iron binding capacity is also low. The red cell life span is moderately shortened and there is an insufficient increase in erythropoiesis. The bone marrow contains decreased, normal, or increased numbers of cells. Hemosiderin appears fuzzy and diffuse. Severe anemia with a marked degree of hemolysis may develop during the course of subacute bacterial endocarditis, Escherichia coli infection, hemolytic streptococcus infection, or Clostridium welchii infection.

Cartwright, G. E., & M. M. Wintrobe: The anemia of infection. XVII. A review. *Advances Int. Med.* 5: 165-226, 1952.

#### 4. ANEMIA OF AZOTEMIA

Anemia commonly develops during the course of renal insufficiency due to any cause. The red cells are normocytic and normochromic, and there is little variation from normal in size and shape. "Acanthocytes" (cells with thorny outpocketings) are occasionally seen. The reticulocyte count is normal, low, or slightly elevated. The bone marrow is normal or hypoplastic. Ferroketic measurements show decreased red cell life span and an inadequate increase in bone marrow erythropoiesis. Hemolysis is occasionally severe, with greatly shortened red cell survival time. Renal failure may be considered responsible for anemia if the NPN is above 75 mg./100 ml., the BUN above 50 mg./100 ml., or the serum creatinine above 2 mg./100 ml.

Loge, J. P., Lange, R. D., & C. V. Moore: Characterization of the anemia associated with chronic renal insufficiency. *Am. J. Med.* 24:4-18, 1958.

## NEOPLASTIC DISEASES OF BLOOD

### ACUTE LEUKEMIA

#### Essentials of Diagnosis

- Weakness, malaise, anorexia, bone and joint pain
- Pallor, fever, petechiae, lymph node swelling, splenomegaly.
- Leukocytosis, immature, abnormal white cells in peripheral blood and bone marrow.
- Anemia, thrombocytopenia

Differentiate from chronic leukemia, idiopathic thrombocytopenic purpura, and aplastic anemia, from infectious mononucleosis, Hodgkin's disease, and lymphosarcoma, and from acute rheumatic fever and malignant bone

tumors. The combination of anemia, thrombocytopenia, and bone marrow proliferation of primitive white cells is found only in acute leukemia

#### General Considerations.

Acute leukemia is a disorder of the blood-forming tissue characterized by proliferation of abnormal white cells. It is generally considered to be neoplastic, occurs in all races, and may develop at any age. Most frequently, however, it develops within the first 5 years of life.

#### Clinical Findings.

**A Symptoms and Signs.** Presenting complaints are often general, consisting of weakness, malaise, anorexia, and fever. Pain in the joints, lymph node swelling, or excessive bleeding after dental extraction may also be initial complaints. Petechiae are frequently seen early in the course of the disease. The spleen and liver may be enlarged.

**B Laboratory Findings.** Normochromic, normocytic anemia occurs early. The platelet count is usually below 100,000/cu mm., while the WBC varies from less than 10,000 to over 100,000/cu mm. On the peripheral blood smear a single immature and abnormal cell type predominates. On a thick or overstained smear it may be mistaken for a lymphocyte.

Auer bodies, red-staining rods in the cytoplasm of myeloblasts or monoblasts, are pathognomonic of acute leukemia. Acute myelocytic leukemia may be differentiated from acute lymphocytic leukemia by the presence of peroxidase-staining cytoplasmic granules in the former.

There is massive proliferation of primitive malignant cells in the bone marrow even when leukopenia exists.

X-ray examination of painful bones may show periosteal elevation. There may also be osteolytic lesions, or a transverse line of radiolucency beneath the metaphyses of the long bones.

#### Complications

Fatal gastrointestinal tract hemorrhage, pressure symptoms on the brain stem, invasion of the CNS, and overwhelming infection are the chief causes of death.

#### Differential Diagnosis

The combination of anemia, thrombocytopenia, and bone marrow proliferation of primitive white cells is found only in leukemia. Leukocytosis may or may not be present. Among the other features, petechiae may be

seen in idiopathic thrombocytopenic purpura or in aplastic anemia but there is no enlargement of lymph nodes liver or spleen Enlarged lymph nodes and splenomegaly may be found in infectious mononucleosis Hodgkin's disease or in lymphosarcoma but the bone marrow and peripheral red cells and platelets are usually normal Marked lymphocytosis is often seen in whooping cough and infectious lymphocytosis but the white cells are mature and RBC and platelet count are normal Malignant tumors e.g. neuroblastoma osteosarcoma and metastatic cancer may cause bone pain anemia and leukocytosis if there is marrow invasion these conditions may resemble leukemia

### Treatment

The treatment of acute leukemia is aimed at symptomatic relief and remission of the disease process

**A General Measures** Once the diagnosis has been established a conference is held with the patient or his family and the nature of the disease its treatment and cost the prognosis and the need for follow up care are discussed in detail It is important that the patient lead as normal a life as possible with maintenance of work or school activities Hospitalization is essential only for transfusions severe complications or terminal involvement

In young patients antileukemic therapy is begun as soon as the diagnosis is established In some elderly patients with only moderate anemia and an aleukemic picture specific antileukemic therapy may not be indicated The antimetabolites are not well tolerated by this group and are not very effective These patients can usually be supported with occasional transfusions for anemia and antibiotics for infection Oral fluid intake must be increased for patients receiving antileukemic agents to prevent precipitation of uric acid crystals in the kidneys

At first patients are followed with weekly blood counts including platelet counts during remissions they are seen every 2-3 weeks

**B Transfusions** Hemoglobin should be maintained at 8-10 Gm/100 ml Whole blood or packed red cells less than a week old are satisfactory

**C Corticosteroids** Regardless of the severity of the disease at the time of diagnosis children and adults are started immediately on prednisolone 10-20 mg 4 times daily (or equivalent cortisone compound) This dose is maintained until a satisfactory clinical and hematologic remission occurs The daily dose is then decreased by 5 mg once a week

**D Antimetabolite Therapy** In addition to corticosteroids mercaptopurine (Purinethol<sup>®</sup>) is given orally in divided daily doses of 2-5 mg/Kg calculated to the nearest 25 mg The effects of this purine antagonist are usually not evident for 3 weeks or more although occasionally it may begin to act within a week L the WBC does not begin to drop within 2 months the medication will probably not be effective

Even in the presence of severe leukopenia mercaptopurine is continued as long as malignant cells remain in the blood or bone marrow Side effects are relatively few but occasionally ulceration of the mucous membranes or hepatitis is seen

Some clinicians alternate mercaptopurine and methotrexate (amethopterin) 1-2.5 mg daily orally or I.M. according to weight in three month periods

Relapses are treated with corticosteroids and mercaptopurine

### E Treatment of Complications

**1 Local manifestations** Severe bone pain massive lymph node enlargement interfering with respirations and swallowing and CNS involvement with signs of increased intracranial pressure may be treated successfully with local irradiation Intrathecal methotrexate 5 ml dissolved in 10 ml of spinal fluid may be a valuable adjunct to oral or I.M. methotrexate

**2 Fever** Careful search is made for a bacterial agent and specific antibiotics are instituted Prophylactic antibiotics are not used

**3 Hemorrhage** Corticosteroids in the above doses and transfusions of fresh whole blood (platelet rich) may be necessary

### Prognosis

Average survival for untreated acute leukemia is about 2-6 months for treated acute leukemia about 6-12 months Patients with acute lymphoblastic leukemia regardless of age and with a WBC of less than 10,000/cu mm have a better prognosis than patients with myeloblastic leukemia In adults remissions of only a few months are generally obtained in children remissions occasionally last from one to several years

Ellison R R Management of acute leukemia in adults M Clin North America 40 743 1956

Zuelzer W W & G Flatz Acute childhood leukemia a ten year study Am J Dis Child 100 886 907 1960



## CHRONIC MYELOCYTIC LEUKEMIA

### Essentials of Diagnosis.

- Weakness, lassitude, fever, abdominal discomfort.
- Painless enlargement of spleen.
- Unexplained leukocytosis, immature white cells in peripheral blood and bone marrow.
- Anemia.

Differentiate from polycythemia vera, myelofibrosis, and leukemoid reactions associated with infection or metastatic cancer.

### General Considerations.

Chronic leukemia is characterized by proliferation of abnormal white cells, which usually invade the blood stream and may infiltrate any part of the body to cause local symptoms. It is considered by many to be a neoplastic process, and progresses slowly but inevitably to death.

In addition to their immaturity, leukemic cells have certain distinguishing biochemical characteristics. Leukemic neutrophilic cells have less glycogen and alkaline phosphatase than normal or polycythemia white cells, whereas their histamine content is higher.

Chronic myelocytic leukemia is primarily a disease of young adults, but it may be found at any age.

### Clinical Findings.

**A. Symptoms and Signs.** Pallor, weakness, sternal tenderness, fever, purpura, skin infiltrations (erythroderma), and retinal hemorrhages or exudate may be seen.

There may be abdominal discomfort secondary to hepatosplenomegaly. Some patients are diagnosed accidentally before the onset of symptoms when a high WBC is found during a routine examination.

**B. Laboratory Findings:** The WBC may exceed 500,000/cu.mm., but fewer than 10% of the cells are "blasts." Nonfilamented neutrophils, metamyelocytes, and myelocytes predominate; the neutrophils are alkaline phosphatase negative, and basophils, eosinophils, and platelets are increased. There is usually some degree of anemia. The cellular elements of the bone marrow resemble the cell types of the peripheral blood.

### Differential Diagnosis.

In leukemoid reactions due to infection, metastatic cancer, or acute blood loss, eosino-

phils and basophils are decreased rather than increased and the alkaline phosphatase reaction of the polymorphonuclear white cells is strongly positive. In myelofibrosis the splenic enlargement is associated with lesser degrees of leukocytosis, the marrow is fibrotic, and the granulocytes are alkaline phosphatase positive.

### Complications

Probably no part of the body is exempt from leukemic infiltration. Complications will depend upon the area infiltrated, e.g., pressure symptoms or hemorrhage if the CNS is infiltrated. The spleen may become very large and painful. Terminally, there may be a "blastic" crisis.

### Treatment

**A. General Measures.** The aim of therapy is palliation of symptoms and correction of anemia. Initial manifestations and each exacerbation should be treated promptly. Specific treatment of the anemia is unnecessary, as it is usually corrected by treatment directed at the leukemic process. Blood counts are checked weekly at first and then once or twice a month until a satisfactory remission is obtained. During remission patients are encouraged to resume normal activity, but follow-up visits are necessary every 1-3 months. The nature of the disease should be explained to the patient and the necessity for periodic observation and lifelong treatment should be impressed upon him.

**B. Irradiation.** X-ray therapy consists of total body irradiation or local therapy to the spleen, liver, or local infiltrates. It is given (by a radiologist) over a period of several weeks and not infrequently there may be some radiation sickness. X-ray is most effective in the treatment of local manifestations.

The results of treatment with radiophosphorus ( $P^{32}$ ) are comparable to those of total body irradiation, it is less effective in the treatment of local manifestations. There is no radiation sickness. The dosage of  $P^{32}$  depends upon the degree of leukocytosis. If the WBC is above 50,000/cu.mm., the initial dosage of  $P^{32}$  is 1-2.5 mc I.V.; 2 weeks later, 1-1.5 mc are given. Similar doses are given every 2 weeks until the white count is less than 20,000/cu.mm. During remission patients are seen every 1-3 months. When the white count rises above 25,000, an additional 1-1.5 mc are given.

**C. Chemotherapy:** Busulfan (Myleran<sup>®</sup>), an alkylating agent, is the drug of choice.

Initial dosage is 2 mg 2-4 times daily continued until the WBC is less than 10 000/cu mm. As a rule the WBC begins to drop within a week and normal values are reached in 4-6 weeks. When the WBC reaches about 10 000/cu mm the drug may be discontinued or administered intermittently. Remissions may last for several months to more than a year. When relapse occurs a course of busulfan may be repeated. Over-treatment results in general depression of myelopoiesis. Irreversible thrombocytopenia may develop. Since thrombocytopenia may occur before any significant drop in hemoglobin, platelet counts should always be done as part of the routine count. The drug should be withheld if platelet values are below normal.

Urethan, mercaptopurine (Purinethol®), colcemid, chlorambucil (Leukeran®), cyclophosphamide (Cytoxan®), triethylenemelamine (TEM), nitrogen mustard, and potassium arsenite (Fowler's solution) have been used in the treatment of chronic myelocytic leukemia.

### Prognosis

The average life expectancy in chronic myelocytic leukemia is about 3-4 years. With appropriate therapy the course is frequently remittent with periods of months during which the patient is free of symptoms. Treatment is palliative only; however, there is no proof that any of the above methods prolong life.

Haut A. & others: Busulfan in the treatment of chronic myelocytic leukemia. The effect of long term intermittent therapy. *Blood* 17:1, 19, 1961.

Haut A., Wintrobe M.M. & G.E. Cartwright: The clinical management of leukemia. *Am J Med* 28:777-83, 1960.

## CHRONIC LYMPHOCYTIC LEUKEMIA

### Essentials of Diagnosis

- Pallor
- Superficial lymph node enlargement
- Unexplained lymphocytosis

Similar lymph node enlargement may be seen in lymphosarcoma and infectious mononucleosis. Differentiation is usually readily made on the basis of the blood smear.

### General Considerations

This is a disease primarily of middle and late adult life. It is very rare in persons

under the age of 20. The onset is insidious and the diagnosis may be made accidentally during routine examination.

### Clinical Findings

**A Symptoms and Signs** Weakness and symptoms of hypermetabolism may be present. Enlarged lymph nodes may cause pressure symptoms (e.g., tracheal compression with respiratory difficulty). The spleen, liver, and lymph nodes are not tender.

**B Laboratory Findings** Anemia varies in severity at the time of diagnosis; the hemoglobin may be normal. Values of 8-9 Gm/100 ml are usually present in the active disease. The first change in the WBC is lymphocytosis. Eventually the WBC rises and may reach 100 500 thousand/cu mm, but the count is lower than in chronic myelocytic leukemia. Over 90% of the cells are mature lymphocytes with very little variation in appearance. There may be some smudge cells. The platelet count tends to be below normal. Early in the disease the marrow architecture is rather well preserved and the marrow contains a fair number of granulocytes and red cell precursors.

### Differential Diagnosis

Lymphocyte counts of 50 100 thousand/cu mm may be seen in children with whooping cough or infectious lymphocytosis. Lymphatic leukemoid reactions of moderate degree (with white counts of 20 30 thousand/cu mm) are occasionally seen with tuberculosis. Diffuse lymph gland enlargement may be found in lymphosarcoma, infectious mononucleosis, tuberculosis, syphilis, carcinomatosis, hypothyroidism, brucellosis, and lupus erythematosus. In Hodgkin's disease, lymph node enlargement is usually asymmetric or only in a single site.

### Complications

Severe hemolytic anemia frequently with a positive Coombs test may develop. Some patients have hypogammaglobulinemia and are susceptible to infection.

### Treatment

**A General Measures** It may be desirable to withhold therapy until clinical manifestations appear or until the leukocyte count approaches 100 000/cu mm. Many older patients with this disorder remain relatively asymptomatic despite high leukocyte levels. All symptomatic patients and all patients with anemia or thrombocytopenia must be treated.

**B. Irradiation:** As for chronic myelocytic leukemia.

### C. Chemotherapy:

1. Chlorambucil (Leukeran®), an alkylating agent, is the treatment of choice. The dosage is 0.1-0.2 mg./Kg. daily in divided doses after meals. Clinical and hematologic improvement may not be evident for 3-4 weeks and maximum improvement may not be achieved for 2-4 months. When the WBC falls below 25,000/cu. mm., the dose should be reduced, usually to a maintenance level of 2-4 mg. daily. The drug should be discontinued when the WBC falls to 5000-10,000/cu. mm. Side effects are relatively uncommon, although gastrointestinal irritation occurs. Pancytopenia may develop, but recovery is prompt when the drug is discontinued.

2. Triethylenemelamine (TEM), 2.5-5 mg. in a single dose on an empty stomach with 1-2 Gm. of sodium bicarbonate, is a useful alkylating agent. It has the advantage of simplicity of administration, but the effects are less predictable than with other agents.

3. Cyclophosphamide (Cytovan®), 2-3 mg./Kg. I.V. daily for 6 days, or 50-100 mg. orally 1-3 times daily, causes less platelet depression than other agents and may be used when other agents have produced thrombocytopenia.

### D. Treatment of Complications.

1. Anemia - Anemia is caused by a combination of 2 factors: increased rate of red cell destruction and inadequate bone marrow compensation. It rarely responds to anti-leukemic therapy and transfusions may have to be given. If hemolysis is prominent, corticosteroids may be needed. Prednisolone (or equivalent), 10-20 mg. 4 times daily, is usually required. With remission of the anemia, corticosteroids may be gradually withdrawn. On rare occasions, with severe hemolytic anemia and splenic sequestration of the red cells, splenectomy may be necessary. Intercurrent anemia due to blood loss is treated with iron.

2. Hemorrhage - Abnormal bleeding in leukemia is usually due to thrombocytopenia, which may be secondary to either the leukemic process or to therapy. If due to the leukemia, it may be improved by appropriate chemotherapy; if due to chemotherapy, the marrow-depressing drugs must be discontinued and steroid therapy instituted until the marrow has had a chance to recover.

3. Infections - Infections are treated with specific antibiotics. Prophylactic use of antibiotics is not recommended. Some patients develop low levels of gamma globulin. With

total globulin levels of less than 1.5 Gm./100 ml. and electrophoretic evidence of depression of the gamma fraction, 10 ml. of gamma globulin should be given I.M. every 2 weeks.

### Prognosis.

The average life expectancy in chronic lymphocytic leukemia is about 3-4 years. Most patients respond well to chemotherapy or x-ray therapy, and long periods of remission are the rule. There is a group of patients with this disorder, usually the more elderly ones, in whom the disease remains relatively inactive without treatment, sometimes for many years.

Houge, C. The early diagnosis and natural history of chronic lymphatic leukemia. *Ann Int Med.* 45 39-55, 1956.

## MULTIPLE MYELOMA

### Essentials of Diagnosis.

- Weakness, weight loss, recurrent pneumonia.
- Constant, severe bone pain aggravated by motion
- Anemia, rapid sedimentation rate, and elevated serum globulin.
- Immature, atypical plasma cells in bone marrow.

Differentiate from malignant or infectious processes. Atypical plasma cells in the marrow, a homogeneous globulin "spike" on electrophoresis, and severe bone pain are usually seen only in multiple myeloma.

### General Considerations.

Multiple myeloma is a malignant disease characterized by plasma cell invasion of the bone marrow and sometimes other organs. Abnormal protein is found in the blood and often in the urine. The type of abnormal protein produced varies with each myeloma patient. In any one patient it will remain the same, however, varying only in quantity.

The disease appears in later life and is twice as common in males as in females. It is seen in all races.

### Clinical Findings.

A. Symptoms and Signs: Symptoms of anemia may be the only complaint, or there may be constant bone pain, especially on motion, and tenderness (especially of the back)

and spontaneous fractures. Spleen and liver are usually not enlarged. Extramedullary plasma cell tumors are occasionally found in the mouth, on the skin, or near the spinal cord. Marked weight loss is common.

**B Laboratory Findings.** Anemia is moderate and of the normocytic, normochromic type. Rouleaux formation is marked and interferes with the technic of the red count, blood smear, typing, and cross-matching. The sedimentation rate is greatly elevated, WBC, platelet count, and morphology are usually normal. The bone marrow may show sheets of plasma cells with large nuclei and nucleoli.

Serum globulin may exceed 10 Gm/100 ml. The electrophoretic pattern is characterized by a tall, sharp peak in contrast to the broad gamma peaks seen in other illnesses with hyperglobulinemia. The abnormal globulin peak may be in the alpha, beta, or gamma range, or it may lie between the beta and gamma peaks (the so-called "myeloma" or "M globulin"). Cryoglobulin, a serum protein which precipitates in the cold, may be found, and a type of amyloidosis may also be present. Serum calcium levels are often elevated, but phosphorus and alkaline phosphatase values remain normal. Nitrogen retention, proteinuria, and renal casts also occur. Bence Jones proteinuria is found in about 40% of myeloma patients.

The bony lesions appear on x-ray as rounded, punched-out, or mottled areas. Sometimes there is merely diffuse osteoporosis. New bone formation is lacking. In about 10% of cases x-rays are normal.

### Differential Diagnosis.

Pathologic fractures and osteolytic lesions are also found in reticulum cell sarcoma, lymphosarcoma, and in metastatic cancer, particularly if the origin is the breast, kidney, prostate, or thyroid. These lesions are usually single, however, and some attempt at new bone formation is evident. Lymphosarcoma is particularly difficult to differentiate from multiple myeloma when there are bony tumors, oral cavity tumors, cord compression with paraplegia, or invasion of the bone marrow by atypical cells. Electrophoresis usually provides the answer.

Hyperparathyroidism is differentiated by low serum phosphorus and high alkaline phosphatase values. In primary macroglobulinemia (Waldenström), the electrophoretic pattern is similar to that of multiple myeloma, but hemorrhagic phenomena are prominent, bone lesions are rare, and the pathologic cells resemble lymphocytes rather than plasma cells.

The diagnosis is made by demonstration of "specific" macroglobulin by serum ultracentrifugation.

In cirrhosis of the liver, cancer, infections, and hypersensitivity reactions, up to 25% of plasma cells may be seen in the bone marrow. Hyperglobulinemia may be seen in sarcoidosis, lupus erythematosus, cirrhosis, lymphopathia venereum, and kala-azar infections. In most of these disorders, however, the basic disorder is obvious, the plasma cells are adult, and the electrophoretic pattern shows a broad gamma elevation rather than a sharp peak.

### Complications.

Complications include paraplegia due to cord tumor, hemorrhage due to interference with the normal coagulation mechanism, recurrent infections due to disturbance of antibody formation, and renal failure without hypertension or hematuria due to renal tubule casts.

### Treatment.

**A General Measures.** Treatment is supportive only, with the principal aims being control of pain and reduction of tumor masses. Antimetabolites are ineffective. Good urine output must be maintained to prevent calculus formation. Ambulation is encouraged to combat negative calcium balance, but patients must avoid exposure to trauma because of their susceptibility to fractures. Frequent blood transfusions may be necessary to combat the anemia. Analgesics may be necessary for control of pain.

**B Irradiation.** X-ray therapy is valuable in controlling pain and decreasing tumor mass.

**C. Urethan.** Urethan is given as 10% eluxar, 4 1/2-1 Gm., 2-4 times daily, or as 1 Gm rectal suppositories, 2 at bedtime. The dose should be large enough, if well tolerated, to maintain slight leukopenia for 7-10 weeks. Subjective improvement and relief of pain may occur within a week, improvement of proteinuria, bone marrow myeloma cells, and hyperglobulinemia takes 6-8 weeks. Side effects are nausea, vomiting, and marrow depression. About one-third of patients will show some improvement.

**D. Cyclophosphamide (Cytoxan®)** is a recently introduced alkylating agent which has been reported to be effective at times in the therapy of multiple myeloma. Give 3 mg./Kg I.V. daily for 6 days followed by 50-100 mg orally 1-3 times daily for maintenance. Side

effects are nausea, alopecia (20%), and leukopenia.

**E. Corticosteroids.** For treatment of fever and hypercalcemia, prednisolone (or equivalent), 10-20 mg. 4 times daily may be tried.

**F. Treatment of Complications.** Hypercalcemia with nausea and vomiting may be combated with methyltestosterone, 100 mg orally daily, or testosterone enanthate in oil (Delatestry<sup>®</sup>), 300 mg. I.M. twice weekly (to cause deposition of excess calcium in the bones), low calcium diet, and corticosteroids. Vertebral fracture and cord compression may require laminectomy and decompression. For recurrent infection it may be necessary to give gamma globulin, 10 ml. I.M. every 2 weeks, in spite of high "gamma globulin" values. Antibiotic therapy is indicated for specific infections.

#### Prognosis.

The average survival time after diagnosis is 1½-2 years. Occasionally a patient may live for many years in apparent remission.

**Osserman, E.F.:** Plasma-cell myeloma, New England J. Med. 281:952-50 and 1006-14, 1959.

### MACROGLOBULINEMIA

Macroglobulinemia is a chronic neoplastic disease of the bone marrow which resembles multiple myeloma and chronic lymphatic leukemia. It occurs most frequently in men over 50. The presenting findings may include weakness, fever, symptoms of anemia, and hemorrhagic phenomena with purpura and ecchymoses. Lymph nodes, liver, and spleen may be moderately enlarged. There may be pancytopenia. The marrow shows replacement with malignant lymphoid cells which bear some resemblance to myeloma cells. Serum globulin is elevated, and the Sia or water test is usually positive. Paper electrophoresis of the serum shows a sharp peak, usually in the gamma region. Definitive diagnosis is made by ultracentrifugation, which shows the abnormal globulin to be of the S (Svedberg) 20 type, implying a molecular weight in excess of one million. Renal involvement is rare. Osteolytic lesions are not seen on x-ray. Macroglobulinemia may be secondary to several clinical disorders, e.g., neoplastic disease, collagen disease, and certain infections.

The treatment is similar to that of chronic lymphatic leukemia. Patients usually survive only for 3-4 years after diagnosis.

**Ritzman, S.E., & others:** The syndrome of macroglobulinemia. Arch. Int. Med. 105. 939-65, 1960.

### MYELOFIBROSIS (Myelosclerosis, Agnogenic Myeloid Metaplasia)

#### Essentials of Diagnosis.

- Weakness and fatigue.
- Large spleen.
- Anisocytosis and poikilocytosis of red cells.
- Leukocytosis.
- "Dry tap" on bone marrow aspiration

Differentiate from chronic myelocytic leukemia, in which the marrow is hyperactive and easily aspirated, hypersplenism, in which the white and platelet counts are low and the marrow is active, and lymphosarcoma, by lymph node or marrow biopsy.

#### General Considerations.

Myelofibrosis is a proliferative neoplastic disorder of the mesenchymal tissue and is probably related to other myeloproliferative disorders such as chronic myelocytic leukemia and polycythemia vera. There is progressive fibrosis of the marrow and myeloid metaplasia in the liver and spleen. The disease is usually seen in adults beyond middle age. In about 10% of cases it is preceded by polycythemia vera. Occasionally it is associated with tuberculosis or metastatic cancer.

#### Clinical Findings.

**A. Symptoms and Signs:** There may be fatigue, weakness, weight loss, occasionally bone pain, abdominal discomfort, and symptoms of anemia. The spleen is almost always enlarged, usually markedly so. The liver is also enlarged. The lymph nodes are not affected.

**B. Laboratory Findings:** Anemia may be severe. The red cells vary greatly in size and shape; teardrop-shaped, distorted red cells, nucleated and stippled cells may be seen. The reticulocyte count is often slightly elevated. The WBC may be high (20-50 thousand/cu.mm.), with a marked shift to the left and many basophils. The white cell alkaline phosphatase re-

action is strongly positive. The platelet count may be greatly increased initially and giant platelets and megakaryocyte fragments may be seen. Bone marrow aspiration is usually unsuccessful yielding only sheets of platelet and megakaryocyte fragments and a few erythroblasts and granulocytes. Bone marrow biopsy shows fibrous tissue replacing normal marrow spaces. Splenic puncture may show erythroblasts, megakaryocytes and young granulocytes.

### Complications

Rapid splenic enlargement may be extremely painful. The patient may develop symptoms of hypermetabolism with fever and sweating.

Secondary hypersplenism may lead to thrombocytopenia and bleeding and to hemolytic anemia with splenic sequestration of red cells. Some patients die in an acute blastic crisis.

### Differential Diagnosis

In chronic myelocytic leukemia the white cell alkaline phosphatase reaction is negative. Hemolytic anemias are readily differentiated by the great number of reticulocytes, hypercellularity and red cell hyperplasia of the bone marrow. Lymphosarcoma and metastatic cancer with dry tap are differentiated by surgical marrow biopsy.

### Treatment

If the spleen is not painful and the anemia only moderate, no treatment may be required. For severe anemia testosterone enanthate (in oil) (Delatestryl<sup>®</sup>) 1-2 mg/Kg twice weekly I.M. may be tried. Many patients have to be maintained on multiple transfusions as for aplastic anemia. For painful enlargement of the spleen give busulfan (Myleran<sup>®</sup>) 2 mg 1-3 times daily or local x-ray radiation. For hemolytic anemia with splenic sequestration give prednisolone (or equivalent) 10-20 mg 4 times daily orally or even consider splenectomy. For blastic crisis mercaptopurine (Purinethol<sup>®</sup>) 2-5 mg/Kg/day may be tried.

### Prognosis

The average survival from the time of diagnosis is 2-3 years. In some patients the disease remains quiescent for several years even without transfusions. Death is due to hemorrhage, secondary infection or acute blastic crisis.

Bouroncle B A & C A Doan. Myelofibrosis. Clinical hematologic and pathologic study of 110 patients. Am J M Sc 243:697 715 1962

## HODGKIN'S DISEASE

### Essentials of Diagnosis

- Regional lymph nodes enlarged, firm, nontender, painless
- Fever, weight loss, excessive sweating, pruritus, fatigue
- Progressive splenomegaly (late)
- Exacerbations and remissions

Hodgkin's disease must be distinguished from other diseases which involve lymph tissue, e.g., tuberculosis, syphilis, brucellosis, infectious mononucleosis, metastatic cancer, leukemia, sarcoidosis, lupus erythematosus and serum sickness. Differential diagnosis is made by biopsy, blood smear or serologic tests.

### General Considerations

Hodgkin's disease is seen in all races; it occurs most commonly in young adults. It is characterized by an abnormal proliferation of many different cells in the lymph nodes: granulocytes (eosinophilic and neutrophilic), lymphocytes, plasma cells, monocytes, histiocytes, fibroblasts and giant cells (Reed-Sternberg). Fibrosis and necrosis may be present and the architecture may be completely obliterated with destruction of the germinal centers of lymphatic tissue. Hodgkin's disease is thought by most clinicians to be a neoplastic disorder, but its histologic features bear a strong resemblance to infectious granuloma.

### Clinical Findings

**A. Symptoms and Signs.** Regional unilateral lymphadenopathy (especially swelling of cervical nodes) is usually the presenting sign. The nodes are firm, nontender and of various sizes. They may adhere to the deeper tissues but the skin remains freely movable. If the mediastinum is involved early respiratory difficulty may be the initial complaint. Hepatosplenomegaly and constitutional complaints usually appear late and there may be fever, excessive sweating, fatigue and pruritus.

**B. Laboratory Findings.** Specific diagnosis is made by biopsy of involved lymphoid tissues. Anemia is a relatively late development. An absolute lymphopenia and eosinophilia are frequently seen.

The bone marrow sections occasionally show nodular infiltrates of the malignant process.

C Osteolytic lesions may be seen on x-ray examination

### Complications

Hemolytic anemia, intractable itching, superior vena cava obstruction and pleural effusion occur. Painful and tender Hodgkin's sarcoma may develop from the primary process.

### Treatment

In general, x-ray treatment is used for localized lesions in asymptomatic patients and chemotherapy is used for patients with generalized or symptomatic disease. Often the 2 methods are combined. Corticosteroids are useful in intractable cases and in the treatment of complications.

A Irradiation. For localized disease in one or several areas without systemic manifestations, 3000-5000 r are given over a period of 3-4 weeks. X-ray is used also as an adjunct to chemotherapy for local irradiation to the mediastinum, CNS, or spleen.

### B Antitumor Chemotherapy

1 Nitrogen mustard - 0.4 mg/Kg of the powder is dissolved in sterile water and given within 5 minutes into an infusion of physiologic saline. Patients are best treated in the evening after a light lunch, no supper, and premedication with sodium phenobarbital, 200 mg (3 gr) and morphine sulfate, 15 mg (1/4 gr). Nausea and vomiting usually occur within 2 hours. Improvement of symptoms and reduction in size of lymph node masses may begin in 1-3 days. Medication may be repeated every 2 months as long as there is no marrow depression.

2 Chlorambucil (Leukeran®) - Used for maintenance following nitrogen mustard therapy in severe cases or instead of nitrogen mustard in less severe cases. Give 0.2 mg/Kg orally in divided doses after meals. Improvement may not begin for 3-4 weeks, and maximum improvement may not be achieved for 2-4 months. Side effects are rare, but medication must be discontinued if bone marrow depression occurs. Patients should be followed with weekly blood counts at first and less frequently thereafter (but at least once a month).

3 Other agents effective in Hodgkin's disease but with no demonstrated advantages over nitrogen mustard include the following:

(1) Triethylenemelamine (TEM) usually given orally, 5 mg for 1-3 days after an overnight fast together with 1-2 Gm of sodium bicarbonate and 2 glasses of water.

(2) Triethylenephosphoramide (Thio-Tepa®), 0.2 mg/Kg daily I/V for 4 days.

(3) Cyclophosphamide (Cytoxan®), 2-3 mg/Kg I/V daily for 6 days followed by 50-100 mg orally 1-3 times daily for maintenance. The principal disadvantage of this drug is the high incidence (20%) of alopecia it causes.

(4) Vinblastine sulfate (Velban®) may be tried in resistant cases. The dosage is 0.1-0.15 mg/Kg I/V once a week depending upon the WBC. Untoward reactions include nausea, mental depression and alopecia.

### C Treatment of Complications

1 Auto-immune hemolytic anemia. See p. 268.

2 Intractable pruritus and fever - Colchicine may be used. Dilute 3 mg in 20 ml of sterile normal saline solution and give very slowly I/V at intervals of 3 days for 3 doses.

3 Pleural effusion. Triethylenemelamine (TEM) may be given locally, 5 mg dissolved in 5 ml of sterile physiologic saline solution and injected into the pleural cavity. After administration the patient's position is changed every 5 minutes for 30 minutes to allow maximum contact of the drug with the pleura.

### Prognosis

The disease is characterized by exacerbations and remissions but is usually fatal within 3 years. Occasionally, relatively benign forms of the disease may remain asymptomatic for many years after initial therapy.

Burchenal J H, & H D Diamond. The leukemias and the lymphomas. Disease A-Month Year Book, Jan 1958.  
Levinson B. A clinical study in Hodgkin's disease. Arch Int Med 99:519-35, 1957.

## LYMPHOSARCOMA

Lymphosarcoma is a malignant disease of lymph node tissue. It may arise in any lymphoid aggregate. As in Hodgkin's disease, the initial manifestation may be a painless enlargement of the superficial lymph glands, particularly in the neck. In contrast to Hodgkin's disease, involvement of the nasopharynx and gastrointestinal tract occurs not infrequently. The diagnosis is made by lymph node biopsy which shows destruction of node architecture and replacement with tightly packed primitive lymphocytes.

This is a disease of middle age, but it may also occur in children. Systemic symp-

toms (anemia and splenomegaly) develop relatively late. The average survival is 2 years.

Therapeutic considerations are the same as for Hodgkin's disease. X-ray treatment is preferred for local manifestations; chemotherapy, especially nitrogen mustard, followed by chlorambucil, is preferred for multiple involvement or systemic symptoms.

Rosenberg S A Diamond H D & L F Craver Lymphosarcoma: the effects of therapy and survival in 1 269 patients in a review of 30 years experience. *Ann Int Med* 53 877 97 1960

### RETICULUM CELL SARCOMA

This disorder resembles lymphosarcoma in many ways; however, the lymph nodes tend to be hard, fixed to the underlying tissue, painful and tender. The diagnosis is made by biopsy showing the predominant cell to be 3-4 times larger than the malignant lymphocytes with abundant cytoplasm. The oropharynx, gastrointestinal tract and bones may be involved. The blood and marrow are usually not affected. There is less tendency to splenic symptoms or marked enlargement of the liver, spleen or mediastinum. The age incidence and prognosis are similar to those of lymphosarcoma. Therapy is the same as outlined for lymphosarcoma and Hodgkin's disease. In general, patients are somewhat less radiosensitive than those with lymphosarcoma.

Lawrence K B & N Lenson Reticulum cell sarcoma. *J A M A* 149 361 2 1952

### GIANT FOLLICULAR LYMPHOMA

In giant follicular lymphoma there is painless enlargement of groups of superficial lymph nodes; they are discrete, rubbery and not fixed. Involvement of the inguinal areas is relatively common. Systemic symptoms are rare and the blood, marrow, spleen and liver are usually not affected. The disease is seen in middle age. It is relatively benign; spontaneous remissions are common and the average survival is 10 years. Chlorambucil or local x-ray irradiation is the treatment of choice.

Rappaport H Winter W J & E B Hicks Follicular lymphoma. *Cancer* 9 792 821 1956

### MYCOSIS FUNGOIDES

Mycosis fungoides is a chronic, fatal disease of the reticuloendothelial cells of the skin which may progress to secondary involvement of lymph nodes and internal organs. Clinical findings include chronic eczema, infiltration, lichenification and plaque formation and tumors. Itching is common. Each stage of the disease may last months to years. The tumors tend to ulcerate.

The disease occurs with equal frequency in men and women, usually between the ages of 35-70. It may affect any part of the body. Macroscopic examination of the lesions shows proliferation of the reticuloendothelial cells; many eosinophils, perhaps some lymphoblasts, fibroblasts and plasma cells.

Treatment may consist of local x-ray radiation or parenteral nitrogen mustard. Dosage considerations are similar to those for Hodgkin's disease.

Kierland R R Cutaneous manifestations of lymphoma including leukemia. *M Clin North America* 1141 8 July 1956

### POLYCYTHEMIA VERA

#### Essentials of Diagnosis

- Malaise, fatigue, weakness
- Florid facies, dusky redness of mucosa
- Greatly increased red cell values and increase in total red cell mass

Polycythemia vera must be differentiated especially from high normal values (see below) which remain relatively stable and do not increase and from stress erythrocytosis, a state of decreased plasma volume, normal red cell volume and rapid fluctuations in blood values seen occasionally in tense individuals.

The upper limits of normal for young male adults are as follows: Hemoglobin 18 Gm/100 ml, RBC



6.2 million, hematocrit, 54 ml./100 ml. For young women: Hemoglobin, 16 Gm./100 ml.; RBC, 5.4 million, hematocrit, 47 ml./100 ml

#### General Considerations.

Polycythemia vera is a myeloproliferative disorder which often involves one or several formed elements, such as red cells, white cells, or platelets in varying degrees. Symptoms are probably due to increased blood viscosity and bone marrow hyperactivity. Although the disease may occur at any age, it is usually a disorder of middle age. It is more common in men than in women.

#### Clinical Findings.

A. Symptoms and Signs: There may be headache, inability to concentrate, some hearing loss, itching (especially after bathing), pain in the fingers and toes, and redness of the conjunctivas. There may be a decreased feeling of well-being and a loss of efficiency and energy. A dusky redness is particularly noticeable on the lips, fingernails, and mucous membranes. The retinal veins are frequently tortuous and black. There is no clubbing of the fingers. The spleen is palpable in about half of cases at initial examination.

B. Laboratory Findings: The RBC is 6-10 million/cu.mm., the hemoglobin is above 18 Gm./100 ml. in men and above 16 Gm./100 ml. in women; and the hematocrit is over 55%. The WBC is normal to 20,000/cu.mm., and there is an increase in basophils. Granulocytes are alkaline-phosphatase positive, platelets may be normal but often are elevated and may be above 1 million/cu.mm.

The bone marrow shows hyperactivity of all elements, the increase in megakaryocytes may be striking.

The arterial oxygen saturation is normal or slightly low. The uric acid is frequently elevated to 5-10 mg./100 ml. The red cell volume is increased above the upper normal of 33 ml./Kg.

#### Differential Diagnosis.

In polycythemia secondary to pulmonary or cardiac disease the basic disorder is usually obvious, as in cyanotic heart disease and pulmonary fibrosis. In marked obesity, which may also result in hypoventilation, the arterial oxygen saturation is distinctly decreased, leukocytosis and thrombocytosis are absent, and bone marrow hyperplasia is limited to the erythroid series. (Emphysema rarely raises the hemoglobin more than 1-2 Gm./100 ml. above normal.)

Polycythemia may occur in association with renal tumors or cysts, pyelonephritis, or renal obstructive disease. Red cells in the urine together with an abnormal elevation of hemoglobin should be investigated by means of I. V. urography. Polycythemia has also been described in association with cerebellar hemangioblastoma and uterine fibroids. In these disorders the spleen is not enlarged and the white cells and platelets are not affected.

#### Complications.

Hemorrhage (particularly gastric hemorrhage) and cerebral thrombosis may occur in uncontrolled polycythemia vera. Excessive bleeding at surgery is common.

#### Treatment

Radiophosphorus ( $P^{32}$ ) is the treatment of choice in most patients. Venesection reduces the red cell volume more quickly, but after initial lowering of red cell values, venesections have to be repeated at intervals of 1-6 months to maintain a sufficiently low hemoglobin level since iron from tissue stores or a normal diet leads to regeneration of blood. Venesection has 3 disadvantages: it creates iron deficiency, which may cause symptoms; it does not treat the hypermetabolism, and it does not lower the platelet count. Venesection is used chiefly in patients under 40 years of age or in conjunction with  $P^{32}$  as initial therapy. In patients with very high hematocrits, Triethylenemelamine (TEM), chlorambucil (Leukeran®), and busulfan (Myleran®) are effective myelodepressants, they are relatively difficult to administer over a prolonged period since they may produce permanent platelet depression.

A. Radiophosphorus ( $P^{32}$ ): Radiophosphorus is the treatment of choice in most patients over 40 years of age and in those who have elevated platelet counts. The initial dosage is based upon body weight: Under 125 lb., 3 mc I. V., 125-155 lb., 4 mc, over 155 lb., 5 mc. If  $P^{32}$  is given orally, the dose is increased by 25%.

After therapy the patient should be seen at intervals of 3-4 weeks until a remission has occurred. Platelets begin to fall at 2 weeks and reach a low point in 3-5 weeks. Red cells begin to decrease at one month and reach a low point at 3-4 months. At 2 months, if there has been no effect on platelets or red cells, patients are re-treated with an additional 2-3 mc. If necessary, another 2-3 mc dose is given at 6 months. When blood counts have returned to normal, patients are re-examined every 3 months.

Remissions may last 6 months to 2 years. Relapse is treated by the total initial effective dose but should not exceed 5 mc.

**B. Venesection (Phlebotomy).** Remove 500-2000 ml. of blood per week until the hematocrit reaches about 50%, and repeat phlebotomy whenever the hematocrit rises 4-5%. The average maintenance is 500 ml. every 2-3 months. When phlebotomy is the only therapy, no medicinal iron must be given. A low-iron diet is not practical, but certain foods of very high iron content should be avoided (clams, oysters, liver, legumes).

**C. Treatment of Complications.** Surgery in patients with polycythemia vera is frequently complicated by hemorrhage. Patients should be in hematologic remission before operation. Blood loss at surgery is replaced by whole blood transfusions. Fibrinogen (human), 4-5 Gm., is given if the bleeding is due to fibrinogen deficiency.

### Prognosis

In a properly treated patient the life span may be normal, there is a tendency to develop myelofibrosis, anemia, and extramedullary hematopoiesis with a very large spleen. Acute leukemia is the cause of death in less than 5% of patients.

Pike, G.M. Polycythemia vera. *New England J. Med.* 258 1250-5 and 1297-1300, 1958

## AGRANULOCYTOSIS

### Essentials of Diagnosis.

- Chills, fever, sore throat, prostration
- Ulceration of oral mucosa and throat.
- Granulocytopenia with relative lymphocytosis.
- Increased sedimentation rate.

Differentiate from aplastic anemia (thrombocytopenia and anemia) and from acute leukemic leukemia (hyperplastic marrow, predominance of malignant cells).

### General Considerations.

Agranulocytosis may be secondary to the use of certain drugs and chemicals, e.g., antithyroid drugs, sulfonamides, phenothiazines, phenylbutazone (Butazolidin<sup>®</sup>), and aminopyrine. Some of these agents lead to the production of circulating agglutinins

against granulocytes; in other cases the cause of agranulocytosis is not known.

### Clinical Findings.

**A. Symptoms and Signs:** Onset is often sudden, with chills, fever, and extreme weakness. There may be a brownish-gray exudate of the throat and greenish-black membranous ulcers of the oral mucosa, respiratory tract, vagina, and rectum. Regional adenopathy is common. Macules and papules developing into bullae may develop on the skin. The spleen and liver are not enlarged, and there is no bone tenderness.

**B. Laboratory Findings:** Granulocytes are selectively depressed with a relative increase in lymphocytes and monocytes. Hemoglobin values and platelet counts are normal. Immature cells are rare. Bone marrow shows agranulocytosis with normal nucleated red cells and megakaryocytes. During the recovery phase immature primitive granulocytes may be seen in peripheral blood smears and bone marrow.

### Complications.

Complications include sepsis, bronchial pneumonia, hemorrhagic necrosis of mucous membrane lesions, and parenchymal liver damage with jaundice.

### Treatment.

**A. General Measures:** Discontinue suspected chemical agents or drugs. Obtain a blood sample for bacterial culture and antibiotic sensitivity testing. Supportive measures include good oral hygiene, adequate fluid intake, and reduction of fever. Patients should be isolated if possible to reduce exposure to infection.

**B. Antibiotics.** Penicillin is the most effective agent against the common invaders, the gram-positive cocci. If there is evidence of bacterial infection, give 0.6-1.2 million units daily while the WBC is low. Penicillin or other antibiotics should not be used "prophylactically." Broad-spectrum antibiotics are used only when specifically indicated on the basis of culture and sensitivity tests.

**C. Corticosteroids:** If the patient appears toxic, corticosteroids may have to be considered.

### Prognosis.

The mortality rate may approach 80% in untreated cases. With antibiotic therapy mortality is much lower and when recovery occurs

it is complete. Patients must be cautioned against re-exposure to offending agents.

Pisciotta, A.V., & others: Agranulocytosis following administration of phenothiazine derivatives. *Am.J.Med.* 25:210-23, 1958.

## HEMORRHAGIC DISORDERS

### Diagnosis of Coagulation Problems.

In the study of a coagulation problem the history is of utmost importance. The following questions must be answered:

(1) How long is the history of bleeding?

Has bleeding been noted since early childhood, or is onset relatively recent? How many previous episodes have there been?

(2) What are the circumstances of the bleeding? Has it occurred after minor surgery, such as tonsillectomy or tooth extraction? Has it occurred after falls or participation in contact sports?

### Coagulation Factor Synonyms

**Factor V:** Proaccelerin, labile factor, Ac globulin.

**Factor VII:** Proconvertin, stable factor, serum prothrombin conversion accelerator (SPCA).

**Factor VIII:** Antihemophilic factor (AHF), antihemophilic globulin (AHG), antihemophilic factor A (AHF-A).

**Factor IX:** Plasma thromboplastin component (PTC), antihemophilic factor B (AHF-B), Christmas factor.

**Factor X:** Stuart factor, Stuart-Prower factor.

**Factor XI:** Plasma thromboplastic antecedent (PTA).

**Factor XII:** Hageman factor.

### Differential Diagnosis of Some Bleeding Disorders

	Hemophilia (AHF, PTC)*		Idiopathic Thrombocytopenic Purpura	Vascular Hemophilia		Thrombasthenia (Glanzmann's)	Prothrombin Complex Deficiency	Fibrinogen Deficiency
	Severe	Mild		A	B			
<b>Clinical Features:</b>								
Petechiae	-	-	++++	+	+	++	Ecchymoses	Ecchymoses
Hematomas, large	++++	++	-	-	-	-	-	-
Hemarthrosis	++++	±	-	±	±	-	-	-
Postsurgical bleeding	++++	++++	+	+++	+++	+	++	+++
Onset in childhood	+	±	-	+	+	+	±	±
Hereditary	+	+	-	+	+	-	-	-
<b>Laboratory:</b>								
Bleeding time	N	N	Incr.	Incr.	Incr.	N or incr.	N	N
Clotting time	Incr.	N	N	N	N	N	N or incr.	No clot
Clot retraction time	N	N	Incr.	N	N	Incr.	N	No clot
Prothrombin time	N	N	N	N	N	N	incr.	Incr.
Thromboplastin screening test	Abn.	Abn.	N	N	Abn.	N	N-abn.	N
Thromboplastin generation test	Decr.	Decr.	Only platelets abn.	N	Abn.	Incr. Only platelets abn.	N	N
Platelet count	N	N	Decr.	N	N	Platelets look abn.	N	N
Tourniquet test (capillary frag.)	N	N	Incr.	N or incr.	N or incr.	N or incr.	N	N

\*AHF = Antihemophilic factor. PTC = Plasma thromboplastin component.

†Frequency expressed on a scale of - to ++++.

(3) What is the duration of the bleeding episode? (Prolonged oozing is more significant than massive hemorrhage.)

(4) Is there a family history of bleeding?

(5) What is the type or character of the bleeding? Purpuric spots suggest a capillary or platelet defect they are not characteristic of hemophilia. Hematomas, hemarthroses, or large ecchymoses at the site of trauma suggest hemophilia. Sudden, severe bleeding from multiple sites after prolonged surgery or during obstetric procedures suggests acquired fibrinogen deficiency. Massive bleeding from a single site without a history of purpura or previous bleeding suggests a surgical or anatomic defect rather than a coagulation defect.

## HEMOPHILIA

### Essentials of Diagnosis.

- Lifelong history of bleeding in a male, usually congenital and familial.
- Slow, prolonged bleeding after minor injury.
- Recurrent hemarthroses and hematomas.
- Prolonged coagulation time, bleeding time normal.

Most of the congenital "bleeders" have classical hemophilia (hemophilia A). The remainder of the group have plasma thromboplastin component deficiency (PTC deficiency, Christmas disease, hemophilia B), plasma thromboplastin (PTA) deficiency, prothrombin<sub>2</sub> complex disorders, or fibrinogen deficiency. Differentiation is based on laboratory tests.

### General Considerations.

Classical hemophilia is due to a deficiency of antihemophilic factor (AHF), a constituent of normal plasma which is essential for thromboplastin formation. The disorder is transmitted as a sex-linked recessive gene by clinically unaffected female carriers to male offspring. AHF levels are decreased in one-third to one-half of female carriers. About 85% of congenital bleeders have classical hemophilia. One-third of these cases are sporadic, i.e., a family history of bleeding is not obtained.

### Clinical Findings.

A. Symptoms and Signs: Patients with hemophilia rarely have massive hemorrhages.

Bleeding is characteristically a delayed and prolonged oozing or trickling, occurring after minor trauma or surgery, e.g., tonsillectomy or tooth extraction. With extravasation of blood, painful hematomas form in the deep subcutaneous or intramuscular tissue. Joint deformity results from repeated hemorrhage into joint spaces. Gastrointestinal bleeding and hematuria are also prominent findings.

The frequency of bleeding episodes is variable. There may be periods of spontaneous bleeding from multiple sites followed by a phase during which there is neither spontaneous bleeding nor bleeding following minor trauma.

In mild cases a bleeding history may be lacking, the disease is suspected only after dental or surgical procedures.

B. Laboratory Findings: In patients with severe hemophilia, the coagulation time may range from 30 minutes to several hours and as much as 90% of residual prothrombin may be found in the serum. Antihemophilic factor (AHF) is virtually absent from the plasma. During clinically silent periods these laboratory tests remain abnormal. Capillary fragility, bleeding time, prothrombin time, fibrinogen content, and platelet values are normal.

In mild cases the coagulation time is normal and the prothrombin consumption may be normal, but the plasma will contain only 5-40% of antihemophilic factor (normal = 50-150%) and thromboplastic screening and thromboplastin generation tests are abnormal.

### Differential Diagnosis.

Plasma thromboplastin component deficiency, which accounts for about 2-3% of congenital bleeders (15% of hemophiliacs) has clinical manifestations and a hereditary transmission identical with those of classical hemophilia. Differentiation is by special coagulation studies.

Plasma thromboplastin antecedent deficiency accounts for 1% of all bleeders. It is transmitted as a dominant trait and affects females as well as males. The clinical course is milder than that of hemophilia; differentiation is made by special coagulation studies.

Prothrombin complex disorders are characterized by a decreased prothrombin time and a normal coagulation time.

In fibrinogen deficiency, there is failure of *in vitro* clot formation or the clot may form at a normal rate and then contract to a tiny residue.

### Complications.

Repeated hemarthroses may lead to ankylosis. Hematoma formation around the

peripheral nerves may cause permanent damage with pain, anesthesia, or muscle atrophy. Retroperitoneal bleeding may be fatal. Auto-immune anticoagulants (anti-AHF) following repeated transfusions develop in less than 5% of patients and are usually fatal.

#### Treatment.

A. General Measures: Treatment is based on raising the level of AHF in the patient's blood and maintaining it at this level until hemostasis is obtained. Since AHF is unstable in vitro and disappears rapidly in vivo, fresh, freshly frozen, or freshly lyophilized normal plasma is the only known effective agent.

Treatment is evaluated by the clinical response. Coagulation time and prothrombin consumption values are invalid as guides during treatment.

The management of PTC deficiency is similar, except that the plasma need not be fresh. PTC is stable at blood bank conditions for long periods.

#### B. Plasma

1. Fresh frozen plasma - Just prior to infusion the plasma is thawed at 37°C. (98.6°F.) until all solid material is liquefied. For maximum response it is administered in a total dose of 10-15 ml./Kg. for the first 24 hours and then in total daily doses of 6-10 ml./Kg. for the next 3-4 days. Smaller amounts may be satisfactory in some cases.

2. Antihemophilic human plasma (irradiated, lyophilized plasma) is supplied in 100 ml. and 250 ml. units, when reconstituted with diluent it is equivalent to plasma. The recommended dose is 1.5-2 ml./lb.

3. Whole blood is less satisfactory as a source of antihemophilic plasma because AHF deteriorates rapidly in bank blood after 24 hours and the volume of transfusion becomes too great.

#### C. Treatment of Complications

1. Hemorrhage following dental extractions - Patients are prepared by infusion of fresh frozen plasma before surgery. Preferably only one tooth, or at most 2 adjacent teeth, are removed at a time. Depending upon various circumstances the socket may or may not be packed with gelfoam, the edges sutured, and the extraction area immobilized with a prefabricated plastic stent. Postextraction bleeding should be treated with local measures, including gauze packs dipped in thrombin. If bleeding is severe, additional plasma or fresh blood should be given.

2. Hemorrhage following surgical procedures - Patients are prepared by infusion of

antihemophilic or fresh frozen plasma before surgery. The death rate following major surgery is more than 30%.

3. Hemarthroses - During the bleeding phase the joint must be put at rest, flexed to the position of comfort, and possibly packed with ice or put into a protective cast. If pain is severe, aspiration may be necessary.

As soon as pain and bleeding have been controlled, usually within 3-5 days, muscle-setting exercises are begun. When swelling subsides, active motion of the joint is encouraged. Weight bearing is not permitted until the periarticular soft tissues have returned to nearly normal and motion and muscle power of the joint are normal.

#### Prognosis.

Spontaneous hemorrhages into joints and bleeding from minor injuries or surgery are rarely dangerous. Major trauma and bleeding into loose tissues, e.g., the retroperitoneal space, may be fatal despite therapy with plasma. Fatal, uncontrollable hemorrhage may also occur if autoimmune anticoagulants (anti-AHF factor) develop following multiple transfusions.

Aggeler, P.M., & others. The mild hemophilias. Occult deficiencies of AHF, PTC and PTA frequently responsible for unexpected surgical bleeding. *Am J. Med* 30 84-94, 1961.

Biggs, R., & R.G. MacFarlane. Haemophilia and related conditions. A survey of 148 cases. *Brit J Haemat.* 4 1-27, 1958.

### IDIOPATHIC (PRIMARY) THROMBOCYTOPENIC PURPURA

#### Essentials of Diagnosis.

- Petechiae, ecchymoses, epistaxis, easy bruising.
- No splenomegaly.
- Decreased platelet count, prolonged bleeding time, poor clot retraction, normal coagulation time.

Thrombocytopenic bleeding is always associated with skin purpura. Massive bleeding without purpura is probably due to some other defect.

In thrombocytopenia due to infections or to drug idiosyncrasy (secondary thrombocytopenic purpura), the purpura remits as soon as the cause is removed. In the thrombocytopenia

which may accompany aplastic anemia, leukemia, and diseases associated with splenomegaly or dysproteinemia, the primary disease is usually evident.

#### General Considerations.

Acute thrombocytopenic purpura occurs most commonly in young children and usually remits spontaneously and permanently within a few weeks. Chronic thrombocytopenic purpura has its onset at any age, and is more common in females. The first symptoms may appear at the menarche or during an incidental infection. The chronic form is characterized by remissions and exacerbations. Occasionally a family history of the disease is obtained.

The spleen is thought to act in this disorder by (1) sequestering already damaged platelets, (2) forming antibodies, or (3) controlling platelet formation by means of a humoral substance which acts on the bone marrow.

#### Clinical Findings.

**A. Symptoms and Signs.** The onset may be sudden, with petechiae, epistaxis, bleeding gums, vaginal bleeding, gastrointestinal bleeding, or hematuria. In the chronic form there may be a history of easy bruising and recurrent showers of petechiae, particularly in pressure areas. The spleen is not palpable.

**B. Laboratory Findings.** The platelet count is always below 100,000/cu mm, and may be below 10,000/cu mm. The absence of platelets on the peripheral blood smear is striking. White cells are not affected, and anemia, if present, is secondary to blood loss.

The bone marrow megakaryocytes are increased in number but not surrounded by platelets; they are abnormal, with single nuclei, scant cytoplasm, and often vacuoles.

The bleeding time is prolonged, but coagulation time is normal. Clot retraction is poor. Prothrombin consumption is decreased in severe cases. Capillary fragility (Rumpel-Leede test) is greatly increased.

#### Differential Diagnosis.

Purpura may be the first sign of acute leukemia. The diagnosis is made by finding the characteristic malignant cells in the blood or bone marrow. In thrombocytopenia accompanying aplastic anemia, the marrow fat is increased and megakaryocytes are decreased or absent. Thrombotic thrombocytopenic purpura is associated with hemolytic anemia, jaundice, and CNS symptoms.

Thrombocytopenic purpura may also be seen in association with a variety of disorders causing splenomegaly: congestive splenomegaly, Gaucher's disease, tuberculosis, sarcoidosis, and myelofibrosis. Lupus erythematosus may be associated with thrombocytopenic purpura with or without splenomegaly.

Nonthrombocytopenic (symptomatic vascular) purpura, occurring in association with a number of disorders, may cause similar skin and mucous membrane lesions. The tourniquet test is usually positive, the bleeding time is often normal, and the platelet count is usually normal but in severe purpura may be moderately reduced. This type of purpura may follow the ingestion of certain drugs, may be seen with severe septicemia, during the course of dysproteinemias, e.g., cryoglobulinemia and macroglobulinemia. Scurvy may cause purpura and massive skin and muscle hemorrhage, especially into the legs and extensor surfaces of the arms. In the Henoch-Schönlein syndrome (anaphylactoid purpura) there is a widespread inflammatory reaction of the capillaries and small arterioles. In addition to purpura there may be abdominal pain and gastrointestinal bleeding, hematuria, and polyarthritides. Vascular hemophilia (Von Willebrand's disease, see p. 299) is characterized by prolonged bleeding time and capillary fragility, platelet count and clot retraction are normal. In thrombasthenia (Glanzmann's syndrome, see p. 295), the platelet count is normal but the platelet morphology is abnormal and clot retraction is poor.

#### Complications.

Cerebral hemorrhage is of special concern, hemorrhage from the nose and gastrointestinal and urinary tracts may be severe or fatal. Pressure of a hematoma on nerve tissue may cause pain, anesthesia, or paralysis. Children born to mothers with idiopathic thrombocytopenic purpura may have transient congenital purpura.

#### Treatment.

**A. General Measures.** Patients should avoid trauma, contact sports, elective surgery and tooth extraction. All unnecessary medications and exposure to potential toxins must be discontinued.

Children with mild purpura following viral infections do not require any therapy. They should be observed until petechiae disappear and the platelet count returns to normal.

**B. Corticosteroids:** Corticosteroids are warranted in patients with moderately severe purpura of short duration, especially when

there is bleeding from the gastrointestinal or genitourinary tract. Steroids are also given to patients with purpura who have complications contraindicating surgery. Prednisolone (or equivalent), 10-20 mg. 4 times daily, is usually required to control bleeding. The dosage is continued until the platelet count returns to normal, and then is gradually decreased at the rate of 5 mg. daily once a week.

**C. Splenectomy.** Splenectomy is indicated for all patients with well-documented thrombocytopenic purpura of more than one year's duration, for all patients with moderately severe purpura who have relapsed 2-3 times after corticosteroid therapy, and for all patients with severe idiopathic thrombocytopenic purpura who do not respond to steroids.

Steroids should not be used immediately before surgery unless there is severe bleeding. If splenectomy must be performed on a patient who has been on steroids, full doses of steroids should be maintained for 3 days after surgery and then decreased as described above.

The platelet count rises promptly following splenectomy, and often doubles within the first 24 hours. Maximum values are reached 1-2 weeks postoperatively. Sometimes the platelet count will exceed 1 million/cu mm before leveling off. Anticoagulant therapy is not necessary.

### Prognosis.

Spontaneous and permanent recovery occurs in 75% of all childhood idiopathic thrombocytopenic purpura and in 25% of all adult cases. Splenectomy is curative in 70-90% of all patients.

Ackroyd, J.F., Allergic purpura. *Am.J. Med.* 14 605-32, 1953.

Doan, C.A., Bouroncle, B.A., & B.K. Wiseman: Idiopathic and secondary thrombocytopenic purpura, clinical study and evaluation of 381 cases over a period of 28 years. *Ann.Int Med.* 53 861-76, 1960

## THROMBOTIC THROMBOCYTOPENIC PURPURA

This is a rare condition characterized by hemolytic anemia, thrombocytopenia, purpura, jaundice, and fever, the patient is sick and drowsy, with fluctuating CNS signs. The onset is acute, prostration is severe, and the disorder is usually rapidly fatal. The disease

may occur at any age, but is seen most frequently in young adults. Splenectomy is of no avail, corticosteroids may be tried.

Clinico-Pathologic Conference Thrombotic thrombocytopenic purpura. *Am.J.Med* 27 115-24, 1960.

## VASCULAR HEMOPHILIA (Pseudohemophilia, Von Willebrand's Disease)

### Essentials of Diagnosis.

- History of excessive bruising and frequent nosebleeds since childhood,
- Prolonged bleeding time, normal platelet count.

This disorder resembles hemophilia by prolonged bleeding, particularly after oropharyngeal surgery or trauma, and also by occasional hemarthroses, however, it occurs in both sexes, the bleeding time is prolonged, and the coagulation time is normal.

### General Considerations.

Vascular hemophilia is transmitted as a mendelian dominant to both sexes, and the hemorrhagic disorder is more severe in females than in males. The hemostatic defect is due to a failure of the arteriole to contract after injury, or there may be an associated deficiency of the antihemophilic factor.

### Clinical Findings.

**A. Symptoms and Signs.** The disease usually appears in childhood and there is often epistaxis, menorrhagia, easy bruising, and postoperative wound hemorrhage, especially after tonsillectomy and tooth extraction. Childbirth, however, is usually uncomplicated by bleeding and frequently these patients can undergo major abdominal surgery without hemorrhagic complications. Skin bleeding is ecchymotic rather than petechial.

**B. Laboratory Findings:** Prolonged bleeding time and increased capillary fragility may be the only abnormalities (pseudohemophilia A), or there may be an associated deficiency of antihemophilic globulin (pseudohemophilia B). Clotting time, prothrombin time, and platelet count are normal.

### Differential Diagnosis.

Vascular hemophilia must be differentiated from thrombaesthesia (Glanzmann's syndrome;

see p. 295), which is also characterized by a prolonged bleeding time and a normal platelet count. In the latter disorder there is a qualitative platelet factor deficiency, prothrombin consumption and thromboplastin generation are impaired, and platelet morphology is abnormal. Sometimes there is poor clot retraction, but prothrombin consumption and thromboplastin generation are normal. Purpura, ecchymoses, and prolonged bleeding time may occur in macroglobulinemia.

#### Treatment.

No specific therapy is available. If the site is accessible, bleeding is controlled by local pressure with thrombin-soaked gel foam. Whole blood replacement may be necessary.

#### Prognosis.

Bleeding is usually self-limited, although it may be prolonged. Fatal bleeding may occur, especially after minor surgical procedures. Childbirth and major abdominal procedures are less likely to be complicated by excessive bleeding.

Spurling, C. L., & M. S. Sacks: Inherited hemorrhagic disorder with antihemophilic globulin deficiency and prolonged bleeding time. *New England J. Med.* 261 311-9, 1959

### ACQUIRED FIBRINOGEN DEFICIENCY

#### Essentials of Diagnosis.

- Ecchymoses and bleeding, spontaneously or after minimal trauma.
- Severe postpartum or postoperative bleeding.
- No in vitro clotting or prolonged coagulation time; abnormal clot retraction.
- Prolonged prothrombin time (Quick).

Unexpectedly profuse or uncontrollable bleeding in certain obstetric and surgical situations suggests acute defibrination. Not only is the blood incoagulable due to the fibrinogen deficiency, but frequently there are associated deficiencies of prothrombin and platelets. Bleeding may be localized at first, but spontaneous bleeding into the skin and mucous membranes may develop as the disease progresses.

#### General Considerations

Fibrinogen deficiency may be caused by lack of production, as in severe liver disease or by excessive utilization, as in prolonged surgery, metastatic cancer, or certain complications of pregnancy. Operative procedures involving the brain or lung, cancer of the prostate, pancreas, or stomach, and amniotic fluid embolism or intrauterine fetal death are conditions in which afibrinogenemia is more likely to occur. In abruptio placentae clot formation at the placental site depletes the fibrinogen supply and results in afibrinogenemia. Rarely, the deficiency may be a congenital and familial (but not a sex-linked) disorder. These patients may be asymptomatic for long periods but will have serious bleeding at surgery and following trauma.

#### Clinical Findings.

A. Symptoms and Signs. The most common manifestations of afibrinogenemia are uncontrollable postpartum hemorrhage and diffuse bleeding from many sites at surgery. Minimal trauma may cause severe bleeding or there may be spontaneous ecchymoses, epistaxis, or gastrointestinal hemorrhage.

B Laboratory Findings. In afibrinogenemia the coagulation time is prolonged indefinitely, but returns to normal with the addition of small amounts of normal plasma or purified fibrinogen (if all other coagulation elements are present). In fibrinogenopenia the blood clot forms at the normal rate, but then retracts to a tiny residue and thus appears to lyse. The Quick prothrombin time is prolonged if the fibrinogen level is less than 125 mg /100 ml. A good semiquantitative test to detect fibrinogen levels of 100 mg or less is the Hyland Laboratories latex fixation test (FI). The Fibrindex® test (Ortho) is not reliable.

#### Differential Diagnosis

Markedly prolonged coagulation time may also be due to severe hemophilia or a circulating anticoagulant. In hemophilia there is a life-long history of joint and muscle bleeding and relatively little ecchymosis. The abnormal coagulation time is corrected by a small amount of thrombin. Circulating anticoagulants may be active against AHF or thromboplastin, or may have heparin-like activity. The bleeding develops suddenly, skin, mucous membrane, and gastrointestinal bleeding are common. When the patient's plasma is mixed with normal plasma, various coagulation tests become abnormal.



### Complications.

Fibrinolysins may become activated. There may be associated prothrombin complex factor deficiency (especially prothrombin and pro-accelerin)

### Treatment.

Treatment consists usually of the I.V. administration of human fibrinogen in amounts sufficient to raise plasma fibrinogen levels to normal (0.2-0.6 Gm /100 ml). Paragon<sup>®</sup> or fibrinogen (human), 4-6 Gm I.V. may raise plasma levels by 100-150 mg /100 ml. In severe cases 10 Gm or more may be necessary.

In cases of intrauterine fetal death, weekly fibrinogen levels should be taken. Hemorrhagic manifestations may appear at any time from 3-6 weeks after fetal death. If the fibrinogen concentration falls below 150-200 mg /100 ml, steps should be taken to deliver the fetus after prior administration of 3-4 Gm of fibrinogen.

Fibrinogen is expensive and may carry the virus of homologous serum jaundice, it should be used only when appropriate tests have demonstrated deficiency.

Whole blood may be necessary to combat shock. Its fibrinogen content is only 200 ml /100 ml of plasma, however, and severe deficiency cannot be repaired in this way.

Uncontrollable postpartum bleeding may require hysterectomy.

### Prognosis.

In fibrinogen deficiency due to liver disease or cancer the prognosis is usually that of the underlying disorder. Excessive bleeding during brain or lung surgery or at delivery may be completely and permanently corrected by I.V. administration of fibrinogen if fibrinolysis has not been activated.

Sacks, M.S.: Fibrinogen deficiency (editorial). *Ann. Int. Med.* 43 1139-46, 1955

## ACQUIRED PROTHROMBIN-COMPLEX DISORDERS

(Factors V, VII, X, & Prothrombin)

### Essentials of Diagnosis.

- Ecchymoses and epistaxis, spontaneously or after minimal trauma,
- Postoperative wound hemorrhage.
- Bleeding from venepuncture.

In all of these disorders an underlying process is usually evident, e.g.,

liver disease or anticoagulant therapy. Regardless of which member of the prothrombin complex is deficient (prothrombin, factors V, VII, or X), the Quick prothrombin time is prolonged. These conditions may resemble purpura (ecchymoses) or hemophilia (prolonged bleeding, hematoma formation).

### General Considerations.

There are 3 forms of prothrombin complex deficiency.

A, Vitamin K Deficiency. This may be seen in obstructive jaundice, in the malabsorption syndrome, after prolonged antibiotic therapy, in hemorrhagic diseases of the newborn, and following continued ingestion, therapeutic or surreptitious, of coumadin anticoagulants. The pattern of vitamin K deficiency is characterized by reduction of factors II, VII, and X but not of factor V.

B, Severe Liver Disease. There is primarily a deficiency of factor V, but factors II, VII, IX, and X may also be low.

C, Excessive Utilization. This may be due to intravascular clotting and may occur in certain obstetric complications, e.g., abruptio placentae, after prolonged surgery of the brain, lung, or prostate, in malignancies, especially of the stomach, pancreas, or prostate, and following hemolytic transfusion reactions. There is a decrease especially of factors V, VIII, fibrinogen, and platelets, and only to a lesser degree of other coagulation factors.

### Clinical Findings.

A, Symptoms and Signs. There is no previous history of hemorrhagic manifestations. Ecchymoses and epistaxis may occur spontaneously or after minimal trauma. Gastrointestinal bleeding and postoperative wound hemorrhage are common. Bleeding into joints does not occur.

B, Laboratory Findings. The Quick prothrombin time measures deficiencies in any member of the prothrombin complex, i.e., if there is a deficiency in prothrombin, factor V, factor VII, or factor X, or if the fibrinogen levels are less than 125 mg./100 ml., the prothrombin time will be prolonged. Conversely, if the prothrombin time is normal one can assume that all prothrombin complex components are adequate. Specific tests for these factors are of value when a congenital defect is suspected or when the underlying cause of the prolonged prothrombin time is not evident.

In these acquired prothrombin complex disorders the prothrombin time is usually below 40-50%, spontaneous bleeding may occur if the prothrombin time falls to 10-15%. Prothrombin consumption, coagulation time, bleeding time, capillary fragility, and clot retraction are normal unless there is associated thromboplastin deficiency.

#### Treatment.

A. General Measures Deficiency due to vitamin K lack or coumarin compound excess is successfully treated by cessation of coumarin therapy and administration of appropriate medication. The deficiency of liver disease, however, does not respond to vitamin K. Replacement therapy with whole blood or plasma is generally unsatisfactory because of the lability of factor V in vitro and the very rapid disappearance rate of factor VII in vivo.

#### B Vitamin K:

1. Phytonadione (fat-soluble vitamin K<sub>1</sub>, Mephyton<sup>®</sup>) for the treatment of coumadin excess - To restore prolonged prothrombin time to normal, give 5 mg. orally. For major bleeding, give 10-15 mg I V slowly at a rate not exceeding 10 mg./minute.

2 Synthetic, water-soluble vitamin K (menadione sodium bisulfite [Hykinone<sup>®</sup>], menadiol [Synkayvite<sup>®</sup>]) is used for the treatment of vitamin K deficiency due to malabsorption. The dosage is 5 mg. daily.

#### Prognosis.

Vitamin K deficiency and the effect of coumarin excess can be corrected by parenteral or oral administration of vitamin K. The prognosis in other conditions depends upon the underlying disorder.

Lewis, J H , & others. Acquired hypoprothrombinemia. Blood 12 84-9, 1957.

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## Gastrointestinal Tract & Liver

John V. Corbone, Sol Silverman, Jr., Milton J. Chotton, & John L. Wilson

### NONSPECIFIC MANIFESTATIONS

#### HALITOSIS ("Bad Breath")

Halitosis can result from many causes, including improper oral hygiene, chronic nasal and sinus disease, dental caries, gum infections, tonsillar infections, systemic diseases, fevers, and toxemias, chronic pulmonary disease (a g., lung abscess), gastrointestinal tract; and neuropsychiatric disorders where only the subjective complaint of "bad breath" is present.

Treatment is directed at the underlying cause.

#### HEARTBURN (Pyrosis)

Heartburn is most frequently a result of dietary indiscretion or of overindulgence in alcohol.

Rule out specific causes, especially diseases of the lower esophagus, stomach, or biliary tract. Antacids are often effective in relieving "sour stomach," although it is not clear that they act by neutralizing gastric hydrochloric acid. Antispasmodic drugs are often of value. A bland diet (see p. 46) should be prescribed.

#### NAUSEA & VOMITING

These symptoms may occur singly or concurrently, and may be due to a wide variety of

causes. Psychic causes may have either a superficial or deep-seated basis. Reflex causes excite the vomiting center by disturbing gastrointestinal structures and other viscera, correction is therefore dependent upon treatment of the underlying cause. Irritation, inflammation, or mechanical disturbances at any level of the gastrointestinal tract (from pharynx to rectum), irritating impulses arising in any diseased viscera, e g., cholecystitis, disturbances of semicircular canals, e g., seasickness, and toxic action of cardiac drugs, e g., digitalis. Central (vomiting center) causes include central emetics (emetine, apomorphine, morphine), exogenous and endogenous toxins, increased intracranial pressure, and cerebral hypoxia due to cerebral anemia or hemorrhage.

#### Treatment.

A. Acute. Simple acute vomiting such as occurs following dietary indiscretion or in the morning sickness of early pregnancy may require little or no treatment. When necessary, treatment consists of prescribing simple tolerated foods and, occasionally, mild sedative and antispasmodic drugs.

B. Prolonged. Severe or prolonged nausea and vomiting requires careful medical management. Specific causes must be corrected. The following general measures may be utilized as adjuncts to specific medical or surgical measures.

1. Fluids and nutrition - Maintain adequate hydration and nutrition. Withhold foods temporarily and give 5-10% glucose in saline solution or water I.V. When oral feedings are resumed, begin with dry foods in small quantities, e.g., salted crackers, graham crackers. With "morning sickness" these foods may best be taken before arising. Later, change to frequent small feedings of simple, palatable foods. Hot beverages (tea and clear broths) and cold beverages (iced tea and carbonated liquids, especially ginger ale) are tolerated quite early. Avoid lukewarm beverages. Always consider the patient's food preferences.

2 Medical measures - Note: It has been suggested that all unnecessary medication be withheld from pregnant women during the critical early phase of fetal development. The possible teratogenic effects of many classes of drugs are now being investigated.

(1) Sedative antispasmodic drugs may be of value.

(2) Chlorpromazine hydrochloride (Thorazine®) and promazine hydrochloride (Sparine®) may be administered deeply 1 M in doses of 25-50 mg every 4-6 hours p r n or orally in doses of 10-50 mg every 4-6 hours p r n.

(3) Prochlorperazine (Compazine®) 5 mg 3-4 times daily orally when feasible, 25 mg by rectal suppository twice daily or 5-10 mg deeply into buttocks every 3-4 hours (not exceeding 40 mg/24 hours), has been reported to be valuable.

(4) Meclizine hydrochloride (Bonine®), 25 mg daily, may be of value in moderate cases.

3 Psychotherapy may be of value if emesis appears to have a psychic basis. Isolation of the patient is recommended if symptoms become chronic. Hospitalization may be necessary. Visiting should be restricted. Avoid unpleasant psychic stimuli such as strange odors, foul-smelling or foul-tasting medication, emesis basins or other unattractive objects, and foods which are improperly prepared or served. Place the patient on a definite treatment program and let it be known that something is being done. "Hard-boiled" or brutal technique are to be avoided. Attempt to determine the psychic basis of the nausea and vomiting but avoid aggressive psychotherapy during the acute phase of the illness.

Cummins, A J. The physiology of symptoms. III Nausea and vomiting. *Am J Digest Dis* (New Series) 3:710-21, 1958.

Moyer, J H. Effective antiemetic agents.

*J Clin North America* 41:465-32, 1957.

### HICCUP (Singultus)

Hiccup, usually a benign, transient phenomenon, may occur as a manifestation of many diseases. It is important to rule out specific causes such as neuroses, CNS disorders, cardiorespiratory disorders, gastrointestinal disorders, renal failure, infectious diseases, and other diseases.

#### Treatment.

Countless measures have been suggested for interrupting the rhythmic reflex that pro-

duces hiccup. None of these may be successful, however, and the symptom may be so prolonged and severe as to jeopardize the patient's life.

A. Simple Home Remedies. These measures probably act by diverting the patient's attention, they consist of distracting conversation, fright, painful or unpleasant stimuli, or of having patient perform such apparently purposeless procedures as holding his breath, sipping ice water, or inhaling strong fumes.

#### B Medical Measures

1 Sedation - Any of the common sedative drugs may be effective, e.g., pentobarbital sodium, 0.1 Gm (1½ gr) orally or 0.13 Gm (2 gr) by rectal suppository.

2 Local anesthetics (e.g., cocaine) may be applied to the nasal mucous membranes or to the pharynx. General anesthesia may be tried in intractable cases.

3 Antispasmodics - Atropine sulfate, 0.3-0.6 mg (½/200-½/100 gr) may be given subcut.

4 Amyl nitrite inhalations may be effective.

5 CO<sub>2</sub> inhalations - Have the patient rebreathe into a paper bag for 3-5 minutes or give 10-15% CO<sub>2</sub> mixture by face mask for 3-5 minutes.

6 Chlorpromazine hydrochloride (Thorazine®) and promazine hydrochloride (Sparine®) have been used successfully for prolonged or intractable hiccup.

C Surgical Measures. Various phrenic nerve operations, including bilateral phrenicotomy, may be indicated in extreme cases which fail to respond to all other measures and which are considered to be a threat to life.

## CONSTIPATION

Specific causes of constipation include colonic or rectal lesions, hypometabolism, and neuroses. Be especially suspicious of organic causes when there are sudden unexplained changes in bowel habits. Inadequate fluids and low-residue diets may have a constipating effect. Constipation is a frequent complication of physical inactivity or prolonged bed rest. The following commonly used drugs may cause constipation: belladonna and derivatives, narcotics, diuretics, salts of bismuth, calcium, and iron, and aluminum hydroxide or aluminum phosphate gels.

## Treatment

The patient should be told that a daily bowel movement is not essential to health or well-being. So-called 'auto-intoxication' theories are unfounded and many symptoms (e.g., lack of "pep") attributed to constipation have no such relationship.

**A Re-establishment of Regular Evacuation**  
Set aside a regular period after a meal (preferably breakfast) for a bowel movement even when the urge to defecate is not present. Cathartics and enemas should not be used for simple constipation since they interfere with the normal bowel reflexes. If it seems inadvisable to withdraw such measures suddenly from a patient who has employed them for a long time, bland laxatives and mild enemas (see below) can be used temporarily. Cathartic and enema 'addicts' often defy all medical measures and treatment is especially difficult when there is a serious underlying psychiatric disturbance.

**B Diet** The diet may be modified to satisfy the following requirements:

- 1 Adequate volume - Often "constipation" is merely due to inadequate food intake.
- 2 Adequate bulk or residue - This does not necessarily imply "roughage" such as bran. Smooth or bland foods may be preferred in spastic constipation.
- 3 Vegetable irritants - Unless there is a specific contraindication (e.g., intolerance) stewed or raw fruits or vegetables may be of value, especially in the 'atonic' type of constipation.
- 4 Adequate fluids - The patient should be encouraged to drink adequate quantities of fluids so that sufficient water will be available in the intestinal tract for passage of intestinal contents. Six to 8 glasses of fluid per day in addition to the fluid content of foods are ordinarily sufficient. A glass of hot water taken one-half hour before breakfast seems to exert a mild laxative effect.

**C Exercise** Moderate physical exercise is essential. Bed patients may require active and passive exercises. Good tone of the external abdominal muscles is important. Corrective physical therapy may be employed in patients with protuberant abdomens.

**D Medications** Bland laxatives may be employed temporarily. They should be withdrawn as soon as the constipation improves.

- 1 Liquid petrolatum (mineral oil) 15-30 ml ( $\frac{1}{2}$ -1 oz) 1-2 times daily p r n. Do not use mineral oil over prolonged periods since

it may interfere with absorption of foods, particularly fat soluble vitamins. There is also a slight risk of lipoid pneumonia even from its oral use.

- 2 Agar with mineral oil 15-30 ml ( $\frac{1}{2}$ -1 oz) 1-2 times daily p r n.

- 3 Olive oil 15-30 ml ( $\frac{1}{2}$ -1 oz) 1-2 times daily p r n.

- 4 Vegetable mucilages e.g. psyllium hydrophilic mucilloid (Metamucil®) 4-12 ml (1-3 dr) 2-3 times daily after meals in a full glass of water.

- 5 Cascara sagrada aromatic fluid extract 4-8 ml (1-2 dr) at bedtime.

- 6 Magnesia magma (milk of magnesia) 15-30 ml ( $\frac{1}{2}$ -1 oz) at bedtime.

- 7 Sodium phosphate 4-8 Gm (1-2 dr) in hot water before breakfast.

- 8 Dioctyl sodium sulfosuccinate (Colace® Dioxinate®) a surface wetting agent in recommended doses varying from 50 to 480 mg/day.

- 9 Bisacodyl (Dulcolax®) a colonic contact laxative 10-15 mg at bedtime.

**E Enemas** Because they interfere with restoration of a normal bowel reflex, enemas should usually be used only as a temporary expedient in chronic constipation or fecal impaction.

- 1 Saline enema (nonirritating) - Warm physiologic saline solution 500-2000 ml p r n.
- 2 Warm tap water (irritating) 500-1000 ml p r n.
- 3 Soapsuds (S S) enema (irritating) - 75 ml of soap solution per liter of water.
- 4 Oil retention enema - 180 ml (6 oz) of mineral oil or vegetable oil instilled in the rectum in the evening and retained overnight. A cleansing soapsuds enema is given the following morning.

## FECAL IMPACTION

Hardened or putty-like stools in the rectum or colon may interfere with the normal passage of feces. If the impaction is not removed manually, by enemas or by surgery, it can constitute partial or complete intestinal obstruction. The impaction may be due to organic causes (painful anorectal disease, tumor or neurogenic disease of the colon) or to functional causes (bulk laxatives, antacids, residual barium from x-ray study, low-residue diet, starvation, drug-induced colonic stasis or prolonged bed rest and debility). The patient may give a history of obstipation but more frequently there is a history of watery

diarrhea There may be blood or mucus in the stool Physical examination may reveal a distended abdomen palpable tumors in the abdomen and a firm stool in the rectum The impaction may be broken up digitally or dislodged with a sigmoidoscope Cleansing enemas (preferably in the knee-chest position) or in the case of impaction higher in the colon colonic irrigations may be of value Daily oil retention enemas followed by digital fragmentation of the impaction and saline enemas may be necessary

## FLATULENCE

Eliminate specific causes of flatulence Gastrointestinal gas is in large part due to swallowed air (aerophagia) However flatulence may be due to dietary causes and functional and organic disease of the digestive system

### Treatment

A Correction of Aerophagia Anxiety states are often associated with deep breathing and sighing and the consequent swallowing of considerable quantities of air When possible treat underlying anxiety features

B Correction of Physical Defects These sometimes interfere with normal swallowing or breathing (1) Structural deformities of the nose and nasopharynx e.g. nasal obstruction and adenoids (2) Spatial defects of the teeth

C Good Hygiene and Eating Habits Instruct the patient to avoid dietary indiscretions eating too rapidly and too much eating while under emotional strain taking laxatives and chewing gum

D Diet The diet should be composed of bland high-protein low-fat low carbohydrate foods Restrict gas producing or irritating foods Foods to be avoided are most raw fruits and vegetables especially cabbage cucumbers onions peppers celery tomatoes and beans sugar in large quantities or in concentrated forms fried foods nuts raisins berries and other seedy fruits spices and alcoholic and carbonated beverages

E Medications Drugs are, in general unsatisfactory, and at times are only of placebo value

1 Antispasmodic sedative drugs are perhaps the most useful of the medications

used for flatulence Besides their antispasmodic sedative effects they serve to diminish the flow of saliva (which is often excessive in these patients) thereby reducing the aerophagia which accompanies swallowing

2 Spirit of peppermint 0.5 ml (7½ min) t i d in a small glass of water after meals

## DIARRHEA

### Etiology

The causes of diarrhea may be classified as follows

A Psychogenic Disorders Nervous diarrhea

B Intestinal

1 Infectious diseases - Viral enteritis amebiasis

2 Exogenous toxins - Heavy metal poisoning

3 Drugs - Catharsis habituation

4 Structural - Gastrocolic fistula

5 Fecal impaction

6 Neoplastic disease - Carcinoma

7 Idiopathic - Chronic ulcerative colitis

C Malabsorption Sprue nontropical sprue

D Pancreatic Disease Pancreatic insufficiency

E Biliary Tract Disorders Cholelithiasis duodenostomy

F Reflex From Other Viscera Pelvic pathology (extrinsic to gastrointestinal tract)

G Neurologic Disease Tabes dorsalis diabetic neuropathy

H Metabolic Disease Hyperthyroidism

I Unknown Cause Diarrhea of travelers

### Treatment

A Eliminate the specific cause whenever possible

B Correct Physiologic Changes Induced by Diarrhea In addition to the necessity for control of hyperperistalsis it is essential that the following secondary or complicating features be treated

- 1 Fluid imbalance (dehydration)
- 2 Mineral imbalance, e g , hypocalcemia
- 3 Nutritional disturbances (e g , hypoproteinemia) and deficiencies
- 4 Psychogenic disturbances, e g , fixation on gastrointestinal tract or anxiety regarding sphincter mishaps in cases of longstanding diarrhea

#### C Diet

1 Nonirritant foods - Most clinicians feel that food should be withheld or that the intake during the first 24 hours should be restricted to liquid foods (See Bacillary Dysentery ) During the acute phase of enteritis only non-irritant foods should be taken by mouth: water, weak tea, rice or barley gruel, meat broth, precooked cereals, toasted bread or soda crackers with butter, and soft-cooked (not fried) eggs. These foods are usually administered in about that same order, as tolerated.

2 Bland foods (never highly spiced or seasoned) - These foods (in addition to the non-irritant foods) should be incorporated in the diets of patients convalescing from acute diarrhea or those with chronic diarrhea: cereals with milk or cream, strained broths and soups, bland cheeses, fish, fowl, meats (not fried), potatoes (not fried), breads, milk products, eggs, and food beverages (not carbonated).

3 Avoid vegetables and fruits (especially raw) fried foods, bran, whole grain cereals, jams, jellies, preserves, syrups and candies, pickles, relishes, spices, coffee, carbonated and alcoholic beverages.

4 Supplementary vitamins - The bland diet is a restricted diet and may further increase the vitamin deficiency induced by altered intestinal absorption. Patients with chronic diarrhea should probably receive vitamins in dosages comparable to those used for chronic vitamin deficiency states. This amount may vary from 4 to 10 times the normal maintenance dose.

#### D Antidiarrheal Agents

1 Bismuth preparations - Any of the following may be used for acute or chronic diarrhea:

- (1) Bismuth subcarbonate, 1-2 Gm (15-30 gr ) after liquid bowel movements or q i d
- (2) Bismuth magma (bismuth hydroxide and subcarbonate), 4 ml (1 dr ) after liquid bowel movements or q i d
- (3)

R Bismuth subcarbonate 15-30 0 (1/2-1 oz )  
Camphorated tincture  
of opium, q s ad 120 0 (4 oz )

Sig Shake well Four ml (1 dr ) after  
liquid bowel movements or q i d

(4) Milk of bismuth and paregoric (equal amounts of each) may be substituted for the above mixture, using the same dose.

#### (5)

R Belladonna extract 0 5 (7 1/2 gr.)  
Bismuth subcarbonate  
Calcium lactate  
Kaolin aa 30 0 (1 oz )  
Peppermint oil 2 drops

Sig 4 ml (1 dr ) t i d , before meals  
and at bedtime or after liquid bowel  
movements as needed (modified after  
Bockus)

2 Pectin-kaolin compounds - Useful proprietary mixtures are available, e g , Kaopectate®. Give 15-30 ml (1/2-1 oz ) t i d before meals and at bedtime, or after liquid bowel movements p r n.

3 Diphenoxylate hydrochloride with atropine sulfate (Lomotil®) 2 5 mg 3-4 times daily p r n , is an effective antidiarrheal agent, but it must be used cautiously in patients with advanced liver disease and in those taking barbiturates and other addicting drugs.

4 Opiates must be avoided in chronic diarrhea and are preferably avoided in acute diarrhea unless there is intractable diarrhea, vomiting and colic. Always exclude the possibility of acute surgical abdominal disease before administering opiates. Give either of the following:

(1) Camphorated opium tincture (paregoric) (not opium tincture) 4-8 ml (1-2 dr ) after liquid movements p r n or with bismuth (see above).

(2) Codeine phosphate 15-65 mg (1/4-1 gr ) subcut after liquid bowel movements p r n.

5 Strong opiates - Morphine and dihydromorphine should be reserved for selected patients with severe acute diarrhea who fail to respond to more conservative measures.

(1) Morphine sulfate, 8-15 mg (1/8-1/4 gr ) subcut after liquid bowel movements p r n. This drug may produce nausea and vomiting.

(2) Dihydromorphine hydrochloride (Dilaudid®) may be substituted for morphine. Give 2-3 mg (1/30-1/20 gr ) I.M. after liquid bowel movements p r n.

6 Antispasmodic and sedative drugs - (See p 323 ) The antispasmodic drugs, particularly when used in combination with the

barbiturates exert a mild antiperistaltic action in acute and chronic diarrheas associated with anxiety tension states. It may be necessary to administer the various belladonna or belladonna-like alkaloids to a point near toxicity in order to achieve the desired effect.

**E Psychotherapy** It is possible that most cases of chronic diarrhea are of psychogenic origin. A survey of anxiety-producing mechanisms should be made in all patients with this complaint.

Kean, B H, & others. The diarrhea of travelers. J A M A 180 367-72, 1962

## PSYCHOLOGIC GASTROINTESTINAL DISORDERS

This common group of disorders has many names, e g, nervous indigestion, functional dyspepsia, pylorospasm, colonic irritability, spastic colitis, functional colitis, mucous colitis, intestinal neurosis and laxative or cathartic colitis. All or a portion of the gastrointestinal tract may be involved. These disorders are characterized by hyperirritability and altered motility and secretion of the gastrointestinal tract and they have a common origin in psychic factors or abnormal living habits (or both).

It is essential to eliminate the possibility of organic gastrointestinal disease. A history of "nervousness, neurotic traits, and emotional disturbances can usually be obtained. The patient's living habits are irregular and unhygienic, e g, improper diet and irregular meals. Bowel consciousness and cathartic and enema habits are a prominent feature. There is a highly variable complex of gastrointestinal symptoms: nausea and vomiting, anorexia, foul breath, sour stomach, flatulence, cramps, and constipation or diarrhea and a definite relationship can usually be established between symptoms and emotional stress or strain.

Examination discloses generalized abdominal tenderness (variable), particularly along the course of the colon. X-ray shows sphincter spasm and altered gastrointestinal motility without other evidence of abnormalities.

### Treatment.

**A Diet** No single diet is applicable to all of these patients but bland diets, in general, are best tolerated. Bland diets may be constipating and "gas-producing" and must be modified to suit individual needs.

**B Personal Habits and Hygiene** Regular hours and meals and adequate sleep, exercise and recreation are important. Restriction of alcohol and tobacco may be indicated.

**C Symptomatic Treatment** Sedative-antispasmodic medication is of particular value in these disorders.

### (1)

R Tincture of belladonna 10-30 0 (1/3-1 oz)  
Elixir of phenobarbital, q s ad 120 0 (4 oz)

Sig 4 ml (1 dr) t i d before meals and at bedtime as needed

### (2)

R Belladonna extract 0 008 (1/8 gr)  
Phenobarbital 0 015 (1/4 gr)

Sig One tablet t i d before meals and at bedtime as needed

**D Psychotherapy** This may consist of simple reassurance or more intensive techniques. Reassurance as to the absence of organic disease, after careful examination is most important.

Jaffe, D S. Psychosomatic mechanisms in constipation and diarrhea. Am J Proct 8 223-8, 1957

Kirsner, J B, & W L Palmer. The irritable colon. Gastroenterology 34 491-501, 1958

## MASSIVE UPPER GASTROINTESTINAL HEMORRHAGE

Massive gastrointestinal hemorrhage is a common emergency. It may be defined as loss of 40% or more of the estimated red cell mass within one week. The 2 immediate objectives of management are to restore blood volume and establish a diagnosis on which definitive treatment can be based.

About 75% of cases are due to peptic ulceration of the duodenum or stomach. Esophageal varices and gastritis are each responsible for about 10% of cases. Gastric neoplasm, hiatal hernia, esophagitis, and miscellaneous disorders account for about 5%.

### Clinical Findings

**A Symptoms and Signs** There is usually



a history of sudden weakness or fainting associated with or followed by tarry stools or vomiting of blood. Melena occurs in all patients, and hematemesis in over 50%. Hematemesis is especially common in esophageal varices (90%), gastritis, and gastric ulcer. The patient may or may not be in shock when first seen but he will at least be pale and weak if major blood loss has occurred.

There may be no pain, and abdominal findings are not remarkable except when hepatomegaly, splenomegaly, or a mass (neoplasm) is present. There may be a past history of peptic ulcer, cirrhosis, or other predisposing disease, but the history may give no clue to the source of bleeding. About half of all patients will have had at least one previous hemorrhage.

The etiology of bleeding should be established promptly, if possible, since the decision whether to operate or to continue with medical measures will often depend upon the diagnosis. The most critical differentiation is between peptic ulcer and esophageal varices, since emergency surgery is frequently indicated and successful in peptic ulcer. Specific diagnosis is of value also because of the difficulties of entering the abdomen in search of an unknown bleeding point.

A history of peptic ulcer, chronic indigestion, or ingestion of antacids favors a diagnosis of peptic ulcer. A history of alcoholism or jaundice favors liver disease. Epigastric tenderness favors peptic disease. Jaundice, hepatosplenomegaly, spider angomas, liver palms, and fetor hepaticus favor liver disease.

**B X-ray Findings** The cause of upper gastrointestinal bleeding can be demonstrated on x-ray in about 75% of cases. When the diagnosis is in doubt, emergency barium examination of the upper gastrointestinal tract should be done immediately. The examination is postponed if the patient is in shock.

**C Esophagoscopy** When varices are suspected in spite of negative x-rays, esophagoscopy is useful. When both varices and peptic ulcer are seen on x-ray, esophagoscopy may help to decide which is bleeding.

## Treatment.

**A General Measures** The patient should be under surgical observation from the outset. Bed rest, mild sedation if necessary, and regular recording of BP, pulse, respiration, temperature, and urine output are instituted. Treatment of shock by blood transfusion is begun without delay. Hematocrit or hemoglobin determinations are done every few hours until stabilized. The objective of blood replacement

is to restore the blood volume. Signs of recovery are slowing of the pulse, return of BP to normal, and elevation of hematocrit to 35% and hemoglobin to 12 Gm /100 ml.

**B Medical Measures** Acid peptic digestion is a causative or aggravating factor in most cases of massive upper gastrointestinal hemorrhage, including varices. Bland feedings and oral medications for ulcer are begun as soon as shock and nausea are controlled. Continued slight bleeding is no contraindication to the following regimen.

1 Diet - Hourly feedings (on the hour) around the clock of 90 ml of milk or milk and cream (Sippy stage I). The diet may be advanced over the next few days as tolerated to puréed bland foods.

2 Antacids Aluminum hydroxide-magnesium trisilicate mixture (Gelusil<sup>®</sup>) or aluminum hydroxide-magnesium hydroxide mixture (Aludrox<sup>®</sup>), 15-30 ml, is given hourly (on the half hour), alternating with the milk and cream mixture.

3 Other medications indicated may include anticholinergics and mild sedation.

**C Management of Bleeding Esophageal Varices** When varices are the cause of bleeding, special measures are indicated (see p 354).

**D Indications for Emergency Operation** Except when esophageal varices are the cause of bleeding, emergency surgery to stop active bleeding should be considered under any of the following circumstances:

1 When the patient has received 1 L. or more of blood but shock is not controlled or recurs promptly.

2 When an acceptable BP and Hct cannot be maintained with a maximum of 500 ml of blood every 8 hours.

3 When bleeding is slow but persists more than 2-3 days.

4 When bleeding stops initially but recurs while the patient is receiving adequate medical treatment.

5 When the patient is over 50. It has been shown that the death rate from exsanguination in spite of conservative measures is greater in the older age group and rare in patients under 40. Massive bleeding is less well tolerated and is less likely to stop in older patients, who will therefore require operative intervention more frequently.

**E Intragastric Cooling** Local gastric hypothermia by means of circulation of cold fluid through an intragastric balloon or lavage with ice water has proved effective in control-

ing massive hemorrhage in certain instances and is worthy of trial in selected cases

### Prognosis

The over-all mortality of about 14% indicates the seriousness of massive upper gastrointestinal hemorrhage. There is great variation in fatality rates depending upon the etiology of the bleeding. Hemorrhage from duodenal ulcer causes death in about 3% of treated cases whereas in bleeding varices the mortality rate may be as high as 50%. The presence of significant cardiac, renal, liver, or other serious systemic disease affects the prognosis in a markedly adverse manner.

Brick, I B, & H S Jeghers. Gastrointestinal hemorrhage (excluding peptic ulcer and esophageal varices). *New England J Med* 253:458-66, 511-8, and 555-60, 1955

Mitty, W F, & others. Factors influencing mortality in bleeding peptic ulcer. *Am J Digest Dis* 6:389-404, 1961

## DISEASES OF THE MOUTH

### CARIES (Dental Decay)

The etiology of dental caries is not known. However, it is well established that 3 essentials are required to produce the lesion: bacteria, a substrate, and a susceptible tooth. Although animal studies indicate a relationship between caries and systemic abnormalities, this has not been confirmed in humans.

The diagnosis is based on x-ray examination (radiolucencies of the enamel and dentin) and clinical observation of an area of tooth structure that is soft, necrotic, discolored, and often sensitive. Both types of examination are necessary to a complete evaluation of the presence and extent of dental caries. There is no absolute correlation between extent of caries and symptoms. Absence of dental pain does not imply absence of caries.

### Prevention & Treatment

Since the cause of dental decay is not definitely known, the following empiric approach is suggested:

A Restorative dentistry to remove decay is the single most important measure. Do not

neglect caries in deciduous teeth, since bone infection or premature loss of these teeth affects the health and eventual positions of the permanent dentition.

B Proper mouth hygiene will reduce bacterial flora and substrate. Frequent brushing with dentifrices and the use of mouth rinses are both helpful. Therapeutic ingredients added to dentifrices have no unequivocal benefits.\*

C Reduction of carbohydrate and sticky foods (e.g., jams, cookies) foods that tend to adhere to tooth surfaces for prolonged periods will reduce available substrate and acid production and decalcification. Coarse foods such as carrots, apples, and celery tend to clean the surfaces of the teeth.

D Topical applications (by a dentist) of stannous fluoride once or twice a year (8% aqueous solution for children and 10% solution for adolescents and adults) will form a more acid-resistant tooth structure (fluorapatite instead of hydroxyapatite). This procedure should be considered if a clinical problem of difficult caries control exists even if the patient has been exposed to a fluoridated water supply during dental development. If water supplies are not fluoridated, daily oral fluoride supplements are recommended during pregnancy and for the child up to age 12 (during tooth development).

Johansen, E (editor). Dental caries. A symposium. *D Clin North America*, July 1962.

### ABSCESSSES OF THE TEETH (Periapical Abscess)

Dental decay is not self-limiting unless it is removed. It will lead to infection of the pulp and subsequent periapical abscess. Death of the pulp and periapical infection may also result from physical and chemical trauma. The only treatment is root canal therapy (cleansing and filling of the entire canal) or extraction.

\*The ADA Council on Dental Therapeutics recently classified Crest® toothpaste (stannous fluoride) under Group B, indicating that there is not sufficient evidence to justify present acceptance but that there is reasonable evidence of its usefulness and safety.

In the early stage of pulp infection the symptoms may not be localized to the infected tooth. Intermittent throbbing pain is usually present, and is intensified by local temperature change. In the later putrescent stage the pain is extreme and continuous, and may be accentuated by heat but is often relieved by cold. After the infection reaches the bone, the typical syndrome is localization, pain upon pressure, and looseness of the tooth. Symptoms may then disappear completely, and, if drainage occurs, a parulis (gum boil) may be the only finding. When drainage is inadequate, swelling, pain, lymphadenopathy, and fever are often present. At this stage antibiotics are advisable before local therapy is undertaken. Diagnosis depends upon symptoms, pulp testing (hot, cold, electricity), percussion, x-rays (may not show the diagnostic periapical radiolucency), looseness, deep decay or fillings, parulis, and swelling. Care should be taken to rule out sinusitis, neuralgia, and diseases affecting the cervical lymph nodes.

Incision and drainage are indicated whenever possible. Antibiotics and analgesics may be given as necessary. Unless sensitivity studies are done, penicillin is the antibiotic of choice. Do not use antibiotic troches.

If not eventually treated by root canal therapy or extraction, the abscess may develop into a more extensive osteomyelitis or cellulitis (or both), or may eventually become cystic, expand, and slowly destroy bone without causing pain.

### VINCENT'S INFECTION (Necrotizing Ulcerating Gingivitis, Trench Mouth)

Vincent's infection is an acute inflammatory disease of the gums which may be accompanied by pain, bleeding, fever, and lymphadenopathy. The etiology is not known, and it is doubtful if the disease is communicable. It may occur as a response to many factors, such as poor mouth hygiene, inadequate diet and sleep, alcoholism, and various other diseases such as infectious mononucleosis, non-specific viral infections, bacterial infections, thrush of mouth, blood dyscrasias, and diabetes mellitus. The presence of fusiform and spiral organisms is of no importance since they occur in about one-third of clinically normal mouths and are absent in some cases of Vincent's infection.

Management depends upon ruling out underlying systemic factors and treating the signs

and symptoms as indicated with systemic antibiotics, oxygenating mouth rinses (3% hydrogen peroxide in an equal volume of warm water), analgesics, rest, and appropriate dietary measures. Refer the patient to a dentist for further treatment (e.g., curettage).

Silverman, S. - The use and abuse of laboratory tests in clinical periodontics. *Academy Review* 8:47-61, 1960.

## PERIODONTAL DISEASE

Food bacteria, and calculi which are present between the gums and teeth in areas called "dental pockets" may cause an inflammatory process and the formation of pus (pyorrhea) with or without discomfort or other symptoms. If this continues unchecked, the involved teeth will become loose and eventually will be lost as a result of resorption of supporting alveolar bone. If there is no drainage, accumulation of pus will lead to acute swelling and pain (lateral abscess).

The diagnosis depends upon a combination of findings including localized pain, loose teeth, demonstration of dental pockets, erythema, and swelling or suppuration. X-ray may reveal destruction of alveolar bone.

As in periapical abscess, the severity of signs and symptoms will determine the advisability of antibiotics. Local drainage and oxygenating mouth rinses (3% hydrogen peroxide in an equal volume of warm water) will usually reverse the acute symptoms and allow for routine follow-up procedures. Curettage or gingivectomy (or both) to reduce excess gum tissue help prevent formation of the "dental pockets" which predispose to acute periodontal infections. In some cases, because of the advanced nature of the lesion (bone loss) or the position of the tooth (third molars in particular), extraction is indicated.

## ULCERATIVE STOMATITIS

Ulcerative stomatitis is a general term for multiple ulcerations on an inflamed oral mucosa. It may be secondary to blood dyscrasias, erythema multiforme, bullous lichen planus, acute herpes simplex infection, pemphigoid lesions, drug reactions, and allergies. Frequently no contributory factor can be identified. A general physical examination and

history are required to establish a diagnosis if possible. Until this is done, treatment should be strictly palliative.

When a causative factor cannot be determined, or if the lesions are not self-limiting, prolonged treatment on an empiric basis may be necessary. The diet should consist of soft bland foods as tolerated, with vitamin supplementation. The use of alcohol and tobacco must be strictly forbidden. Mild mouth washes, preferably salt solution (4 times a day and after meals), promote optimal hygiene and relieve discomfort. Potassium permanganate, 1:10,000 solution may also be used. Give analgesics as necessary for pain.

### APHTHOUS ULCER (Canker Sore)

An aphthous ulcer is a shallow mucosal ulcer with flat, fairly even borders surrounded by erythema. The ulcer may or may not be covered with a pseudomembrane. It has never been adequately demonstrated that this lesion is due to a virus or any other specific chemical, physical, or microbial agent. One or more ulcers may be present, and they tend to be recurrent. They are often painful. Nuts, chocolate, and irritants such as citrus fruits are often said to cause flare-ups of aphthous ulceration, but abstinence will not prevent recurrence. Stresses of various types have also been shown to be contributory. The diagnosis is seldom clearly established, but depends mainly upon ruling out similar but more readily identifiable disease, a history of recurrence, and inspection of the ulcer.

Bland mouth rinses and hydrocortisone-antibiotic ointments reduce pain and encourage healing. Hydrocortisone in an adhesive base (Orabase<sup>®</sup>) has been particularly useful. Sedatives, analgesics, and vitamins may help indirectly. Vaccines and gamma globulin have not proved significantly beneficial. Although caustics relieve pain by cauterizing the fine nerve endings, they also cause necrosis and scar tissue, which prolong healing and often prepare the site for chronic recurrences. Systemic antibiotics and corticoids are contraindicated.

Healing, which usually occurs in 1-3 weeks, may be only slightly accelerated with treatment.

### CANDIDIASIS (Moniliasis, Thrush)

Thrush of the mouth is due to overgrowth of *Candida albicans*. It is characterized by creamy-white, curd-like patches anywhere in the mouth. The adjacent mucosa is usually erythematous, and scraping the lesions usually uncovers a raw bleeding surface. Pain is commonly present, and fever and lymphadenopathy are sometimes present also. Although this fungus occurs in about one-third of normal appearing mouths, overgrowth does not occur unless the "balance" of the oral flora is disturbed, e.g., by debilitating or acute illnesses or as a result of anti-infective therapy. Concomitant candidiasis of the gastrointestinal tract may occur.

The diagnosis is based upon the rather typical clinical picture, and may be confirmed by cultures.

Treatment is not uniformly successful, the infection usually persists in spite of treatment as long as the causative factors are present. The patient should have a nutritious diet with vitamin supplementation, and should receive sufficient rest. Saline solution mouth rinses every 2 hours give local relief and promote healing. Specific antifungal therapy consists of nystatin (Mycostatin<sup>®</sup>) mouth rinses 500,000 units t.i.d. (100,000 units/ml in a flavored vehicle), held in the mouth and then swallowed, and 1% aqueous gentian violet solution painted on affected areas t.i.d.

### LEUKOPLAKIA

Leukoplakia (a white patch) of the oral mucous membranes is occasionally a sign of carcinoma; it is important to rule out malignancy.

The most common cause of leukoplakia is epithelial hyperplasia and hyperkeratosis usually in response to an irritant. Such conditions as white spongy nevi and lichen planus can be confused with leukoplakia, but they have no malignant tendencies. Keratosis of the tongue is often a finding in tertiary syphilis and there is a significant statistical correlation between cancer of the tongue and a history of syphilis. In many cases the cause cannot be determined.

Because there is no reliable correlation between clinical features and microscopic findings, a definitive diagnosis may be established only by histopathology. Since the white patch occurs so frequently that routine biopsy

sies may be impractical, careful clinical examination and follow-up and cytologic smears are essential.

Treatment consists of removing all irritants (e.g., tobacco, ill-fitting dentures) and excision of the white patch. Electrodesiccation, vitamin A, and proteolytic enzymes have not given predictably favorable results.

Silverman, S., & W.H. Ware: Comparisons of histologic, cytologic and clinical findings in intraoral leukoplakia and associated carcinoma. *Oral Surg.* 4:412-22, 1960.

### SIALADENITIS

Acute inflammation of a parotid or submandibular salivary gland is usually due to viral or bacterial infection or, less commonly, blockage of the duct. The gland is swollen and tender. Observation of Wharton's and Stenson's ducts may show absent or scanty secretion with fluctuation of swelling, especially during meals, which indicates blockage, or a turbid secretion, which suggests infection. Clinical examination and x-ray may disclose ductal or glandular calcific deposits. Sialograms are of help in differentiating normal and diseased glands. Probing the ducts may reveal an inorganic plug or organic stenosis.

Inflammation of the salivary glands due to bacterial, chemical, or other unidentified factors may also cause xerostomia. When the dryness is not responsive to therapy and acute signs are not apparent, systemic sialogogues or local troches may stimulate salivation.

Tumors may be confused with nonneoplastic inflammation. In these situations a biopsy should be performed, but only after other diagnostic and therapeutic procedures have failed to yield a diagnosis. Neoplasms are usually not associated with an acute onset and, at least in the early phases, are not painful. The lymph nodes are intimately associated with the salivary glands, and consideration must be given to diseases in which lymphadenopathy is a prominent finding, e.g., lymphomas and metastatic malignancy. Such lesions as glandular hyperplasia and Mikulicz's disease may be confused with salivary or parotid gland disorders. The cause is not known, and no treatment is required.

In the acute stage, antibiotics, heat, and analgesics are indicated. Ductal stones which are too large for removal by massage and manipulation must be removed surgically (when the acute phase has subsided). If calcification

or infection of the gland recurs often, extirpation of the gland must be considered. Radiation therapy is often effective in curing acute or recurrent sialadenitis which does not respond to other types of therapy.

### GLOSSITIS

Inflammation of the tongue (usually associated with partial or complete loss of the filiform papillae, which creates a red, smooth appearance) may be secondary to a variety of diseases such as anemia, nutritional deficiency, drug reactions, systemic infection, and physical or chemical irritations. Treatment is based on identifying and correcting the primary cause if possible and palliating the tongue symptoms as required. Many obscure cases are due to such idiopathic conditions as geographic tongue and median rhomboid glossitis.

The diagnosis is usually based on the history and laboratory studies, including cultures as indicated. Empiric therapy may be of diagnostic value in obscure cases.

When the cause cannot be determined and there are no symptoms, therapy is not indicated.

### GLOSSODYNIA, GLOSSOPYROSIS

Burning and pain, which may involve the entire tongue or isolated areas and may occur with or without glossitis, may be associated findings in hypochromic or pernicious anemia, nutritional disturbances, diabetes mellitus, or other disorders, and may be the presenting symptoms. In those cases due to diabetes the two-hour glucose tolerance test is often positive when the screening urinalysis is negative. Allergens (e.g., in dentifrices) are rare causes of tongue pain. Certain foods may cause flare-ups, but are not the primary causes. Dentures, poor oral hygiene, and dental infections are usually of no etiologic significance.

Although most cases occur in postmenopausal women, these disorders are not restricted to this group and are not benefitted by steroid therapy.

In most cases a primary cause cannot be identified. Cultures are of no value since the offending organisms are usually present also in normal mouths. Many clinicians believe that these symptoms occur on a primarily functional basis.

Treatment is mainly empiric. Antihistamines, sedatives and tranquilizers and vitamins are occasionally of value. The injection of hydrocortisone in an oil base directly into the tongue has been of some help in puzzling cases. Local anesthetic injections and placebo injections are of value in differentiating functional and organic disease. Ointments and mouth rinses are of no value.

Partial xerostomia occasionally contributes to the symptoms. This may be remedied by sucking on nonmedicated troches or the administration of pilocarpine 10-20 mg (1/6-1/3 gr) daily in divided doses.

Cheraskin E. The problem of diabetes mellitus in dental practice. *J Dent Med* 15:67 79 1960.

### PIGMENTATION OF GINGIVAS

Abnormal pigmentation of the gingiva is most commonly a racially controlled melanin deposition in the epithelial cytoplasm. It is most prevalent in non-Caucasian peoples. The color varies from brown to black and the involvement may be in isolated patches or a diffuse speckling. Nongenetic causes include epithelial or dermal nevi (rare), drugs (e.g. bismuth, arsenic, mercury or lead) and amalgam fragments which become embedded in the gums during dental work. Similar lesions may also appear during the menopause or in Addison's disease, intestinal polyposis, neurofibromatosis and several other disorders associated with generalized pigmentations.

The most important consideration is to rule out malignant melanoma (extremely rare in the mouth) which is suggested by rapid growth and slight elevation.

### GINGIVAL HYPERTROPHY

Gingival hypertrophy or enlargement is usually due to epithelial and fibroblastic hyperplasia. Erythema, hemorrhage and pain are not usually present. (This is in contrast to acute or subacute gingivitis, an inflammatory process usually caused by bacterial infection and poor oral hygiene, see Vincent's Infection.) It may be congenital (gingival fibromatosis) or it may be due to a drug reaction (commonly to diphenylhydantoin or one of the other anti-

convulsants). In many instances the cause cannot be determined.

If the hyperplasia cannot be reversed by correcting a causative factor and if a problem of hygiene or tooth movement is present, gingivectomy is indicated. Recurrence is common.

## DISEASES OF THE ESOPHAGUS

### CARDIOSPASM & ACHALASIA OF THE ESOPHAGUS

Cardiospasm is an idiopathic neuromuscular disturbance resulting in dilatation of the esophagus without organic stenosis. It causes severe but often intermittent swallowing difficulties. Although the peak onset is in men between the ages of 20 and 40, cardiospasm may occur in both sexes at any age.

There seem to be 2 types of achalasia of the esophagus. They can be recognized by characteristic differences in symptomatology, x-ray findings and pathologic findings at surgery. The more common type exhibits a narrowing within the distal 5 cm (2 inches) of the esophagus. The esophagus above is widely dilated and its muscle layer greatly thickened. The esophagus may assume a sigmoid configuration. This type of achalasia is usually painless and the esophagus appears atonic after a barium swallow. These patients are prone to pulmonary complications (atelectasis, pneumonia and fibrosis) as a result of repeated aspiration of stagnant esophageal contents.

The second variety of achalasia is characterized by hypertrophy of the circular muscle layer in the lower esophageal segment. The esophagus is only moderately dilated. These patients experience retrosternal pain as an early or persistent symptom. On fluoroscopic examination the esophagus appears hypertonic; i.e., peristaltic activity is increased and disordered.

Obstruction to the passage of both liquids and solids results in difficulty with swallowing and regurgitation of food (food seems to stick at the level of the xyphoid), aggravated by extremely cold or hot liquids, carbonated beverages or emotional upset. Obstruction may be transient or may last for days, stretching, deep breathing or exercise may relieve it.

Pain is generally located at the xyphoid, but may radiate to the back substernally and to the neck, and may occur with or without swallowing.

X-ray of the esophagus reveals a smooth obstruction at the cardia with dilatation of the esophagus above the area of stenosis. Peristaltic waves are small and irregular.

If the patient with achalasia is given 1-5 mg of methacholine (Mechohyl<sup>®</sup>), 1 M, the esophagus will undergo violent tonic contractions. This response is not seen in normal individuals or patients with other esophageal lesions.

Aspiration of regurgitated material may cause pulmonary infections or even strangulation. Because of difficult alimentation malnutrition may result.

Treatment consists of administration of soft or liquid foods until definitive treatment is possible. Brusque dilatation of the cardia with a pneumatic dilator or a myectomy may be indicated.

Ingelfinger, F J Disorders of esophageal motor functions. *Advances Int Med* 8 11 40, 1956

Kramer, P., & F J Ingelfinger Cardio spasm a generalized disorder of esophageal motility. *Am J Med* 7 174-9, 1949

## ESOPHAGEAL WEBS

Congenital webs may occur at various levels of the esophagus, causing narrowing and the symptoms and signs of obstruction. The webs are demonstrable by esophagoscopy or x-ray, or may be seen at surgery. Upper esophageal webs may be associated with anemia (Plummer-Vinson syndrome), which is manifested by dysphagia, glossitis, spooning of nails, splenomegaly, and hypochromic anemia. Treatment consists of division of the webs by bougienage, esophagoscopy, or occasionally, surgery. Iron deficiency anemia, when present, is treated with iron salts.

Shamma's, M H, & E B Benedict Esophageal webs a report of 58 cases and an attempt at classification. *New England J Med* 259 378-84, 1958

## LOWER ESOPHAGEAL RING

An anatomic ring in the lower esophagus causes intermittent dysphagia of solid food when the lumen of the esophagus is decreased to 14 mm ( $\frac{3}{4}$  inch) or less in diameter. X-ray shows a clearly defined diaphragm-like narrowing of the distal esophageal lumen. Anatomic studies reveal this diaphragm to be located at the esophagogastric junction.

If symptoms are present, rupture or surgical division of the ring is indicated.

Schatzki, R, & J E Gary The lower esophageal ring. *Am J Roentgenol* 75 246-61, 1956

## ESOPHAGEAL CYSTS

Esophageal cysts probably result from buds of the primitive foregut or tracheobronchial branches. They may be asymptomatic but can cause dysphagia, dyspnea, cough, cyanosis, or chest pain, either because of their location or because they tend to contain acid-secreting epithelium which may produce peptic ulceration. The cysts are in the lower half of the esophagus between the muscle layers of the esophageal wall. Diagnosis is made by demonstration of a mediastinal mass on x-ray or at surgery. Surgical excision may be necessary.

Desfornea, G, & J W Strieder Esophageal cysts. *New England J Med* 262 60-64, 1960

## DIVERTICULUM OF THE ESOPHAGUS

### Essentials of Diagnosis

- Dysphagia progressing as more is eaten, bad breath, foul taste in mouth
- Regurgitation of undigested or partially digested food representing first portion of a meal
- Irritable cough
- Swelling in neck with eating
- Increased salivation
- Gurgling
- X-ray confirms diagnosis

The dysphagia and regurgitation associated with a diverticulum must

be distinguished from that caused by neoplasm, strictures, or spasms of the esophagus, usually on the basis of the x-ray examination or the presence of a mass in the neck after eating

### General Considerations.

Diverticula are classified as true or pulsion diverticula, which occur at either end of the esophagus (most commonly at the hypopharynx), or false or traction diverticula, located in the middle third of the esophagus (at the level of the left main bronchus) adjacent to hilar lymph nodes. Pulsion diverticulum is a herniation of the mucosa, due to internal pressure, through a weakness in the muscle wall of the esophagus either at the pharyngoesophageal junction (inferior pharyngeal constrictors) or the epiphrenic region. Traction diverticulum is usually due to external traction on a normal esophageal structure by inflammatory adhesions. It does not cause symptoms and is an incidental x-ray finding. Pulsion diverticulum usually causes symptoms. Pulsion diverticulum may also occur as a result of a local esophageal injury, e.g., a lye burn.

### Clinical Findings.

**A. Symptoms and Signs.** Symptoms and signs are related to the size of the diverticulum, the amount of food stasis that occurs, and the compression of nearby structures. Small diverticula are usually asymptomatic. The principal symptom is dysphagia due to increased mucus in the throat. The initial portion of a meal is generally swallowed well, but filling of the diverticulum causes pressure distress. Undigested food is then regurgitated. In small diverticula this may occur only on lying down. Swelling of the neck after eating and gurglings in the neck may occur. Halitosis and a foul taste in the mouth may be present. In the late stages weight loss may occur.

**B. X-ray Findings.** X-ray demonstration of the posterior diverticulum at the junction of the hypopharynx and esophagus is diagnostic of a pulsion diverticulum. Other diverticula are also readily demonstrated on x-ray examination.

### Treatment & Prognosis

Surgical removal of the offending pouch is usually curative. If untreated, dysphagia progresses and pulmonary complications (due to aspiration of regurgitated material) and mediastinitis may occur.

Mendi, K., & C.J. Evans. Congenital and acquired diverticula of the esophagus. *Brit J. Radiol.* 35:53-8, 1962

### PEPTIC ESOPHAGITIS

Peptic esophagitis is related to reflux of gastric juices into the esophagus. Gastric reflux is counteracted by saliva and the alkaline secretion of the esophageal glands. Peptic esophagitis is believed to be due to the fact that the acid-pepsin activity of gastric juice destroys the effectiveness of the protective mechanisms of the esophagus. Contributing factors may include (1) unusual anatomic location of the cardia (short esophagus), (2) obstruction to outflow of the stomach with regurgitation proximally, (3) hiatus hernia, and (4) excessive vomiting.

Manifestations include dysphagia, substernal pain, and hypochromic anemia. Stricture and hemorrhage are late complications.

When the peptic disease is the important factor, dietary and medical treatment should be similar to that for peptic ulcer. The patient should be instructed to sleep in a semi-reclining position to prevent gastric reflux. Esophagitis associated with a small hiatus hernia should be similarly treated, esophagitis associated with a large hiatus hernia, however, usually requires surgical repair. Peptic esophagitis associated with short esophagus, stricture or traction type hiatus hernia often requires dilatation in addition to the ulcer regimen. In intractable cases attempts to decrease gastric acidity by x-ray to the stomach, vagotomy, partial gastrectomy, esophagojejunostomy, and actual resection of the strictures may give relief.

Ballum, C.M., & others. The diagnosis of esophagitis. *Am J Digest Dis* 5:88-93, 1960

Cross, F.S., & E.B. Kay. The etiology and treatment of peptic esophagitis. *Ann Surg* 143:360-8, 1956

McHardy, G., McHardy, R., & C.E. Craighead. Erosive esophagitis. *GP* 16:74-83, 1957

Lahey, F.H., & K.W. Warren. Esophageal diverticula. *Surg Gynec. & Obst* 93:1-26, 1954.



## BENIGN STRICTURE OF THE ESOPHAGUS

Healing of any inflammatory lesion of the esophagus may result in a cicatricial stricture. Common causes are ingestion of corrosive substances, acute infectious diseases, foreign body or instrumentation injuries and peptic esophagitis.

The characteristic symptom is slowly progressive dysphagia. In corrosive burns the acute phase may be followed by a few weeks of improvement before the stricture becomes severe. Ability to swallow liquids is maintained longest.

Pain may occur and the sensation of food sticking in the chest is common. Localization of these sensations at the level of the lesion is often surprisingly accurate. X-ray demonstration of smooth narrowing with little or no dilatation above is characteristic. Esophagoscopy with biopsy may be required for confirmation in doubtful cases.

Careful dilatation with a string-guided bougie or a hydrostatic dilator is usually successful. However, dilatation requires skill and experience if symptoms cannot be relieved by this means. Resection of the stricture and esophagogastrostomy are indicated.

Benedict, E. B., & J. E. O. Gillespie. Esophageal stenosis caused by peptic esophagitis or ulceration. *New England J Med* 250: 642-51, 1954.

## HIATUS HERNIA

### Essentials of Diagnosis

- Pressure sensation, severe pain burning behind lower sternum (any or all 3)
- Pain aggravated by recumbency or increase of abdominal pressure, relieved by upright position
- Cough, dyspnea, palpitation and tachycardia may be present
- X-ray and esophagoscopy demonstrate the herniation

The retrosternal pain of hiatus hernia may radiate into the neck and arms and require differentiation from the pain of ischemic heart disease. Hiatus hernia may be an asymptomatic incidental finding.

### General Considerations

Herniation of a portion of the stomach through the diaphragm can be divided into 2 types: paraesophageal and short esophageal. In paraesophageal hernia the esophagus is of normal length and herniation occurs through a large esophageal hiatus. In the short esophageal type (due to congenital or acquired esophageal shortening) a portion of the gastric cardia is pulled through the diaphragm. Either type may be asymptomatic. Symptoms usually occur in older or obese people or those who undergo a sudden gain in weight.

### Clinical Findings

**A Symptoms and Signs.** Distention of the pouch with air or food causes a pressure sensation or severe pain behind the lower sternum which may radiate to the jaw and arms. The pain is precipitated by increase in abdominal pressure due to coughing, lifting, bending, eating or lying down. It is relieved by getting up or belching. Regurgitation of the stomach contents causes symptoms of peptic esophagitis. Pulmonary or cardiac symptoms such as tachycardia, palpitation, cough and dyspnea may occur with large hernias.

**B X-ray Findings.** X-ray demonstration of the hernia (with the patient in the Trendelenburg position or with abdominal compression) is usually possible.

**C Esophagoscopy** is of aid in diagnosis and better demonstrates associated esophagitis.

### Complications

Hemorrhage may occur from erosions or ulceration in the thoracic pouch.

### Treatment

Treatment is as for functional dyspepsia. Small frequent feedings of bland, easily tolerated foods and antispasmodic-sedative medication. Antacid powders frequently provide relief from heartburn. The patient should be instructed to avoid lying down immediately after eating and to avoid exercising vigorously after eating. He should sleep in the semi-Fowler position or at least with upper part of body slightly elevated.

Surgical correction of the hiatal defect is an extensive procedure which should be considered only if the symptoms are progressive and severe and fail to respond to conservative management.

### Prognosis

Dietary management and weight reduction usually relieve the symptoms. Surgical re-

pair may be required for large hernias which cause severe symptoms

Edmunds V Hiatus hernia a clinical study of 200 cases Quart J Med 26 445 65 1957

Keefer C S The diaphragm some reflections on its function and its diseases Bull Johns Hopkins Hosp 100 147 72 1957

### BENIGN NEOPLASMS OF THE ESOPHAGUS

Benign neoplasms of the esophagus occur infrequently Long standing nonprogressive dysphagia is the only symptom and must be differentiated from other causes of dysphagia such as stricture diverticulum cardiospasm and hysteria Esophagoscopy and x ray findings are often diagnostic The lesion itself must be differentiated from malignant neoplasm by biopsy

Surgical resection of the tumor is curative

Totten R S & others Benign tumors and cysts of the esophagus J Thoracic Surg 25 606 22 1953

### CARCINOMA OF THE ESOPHAGUS

#### Essentials of Diagnosis

- Progressive dysphagia
- Pain and a sensation of lump at times at the exact site of the lesion
- Late occurrence of regurgitation belching hoarseness cough
- X ray or esophagoscopy evidence of obstruction
- Biopsy proves diagnosis

Carcinoma of the esophagus must be differentiated from cardiospasm diffuse esophageal spasm and strictures The x ray picture may be similar to that found with spasm and stricture and final differentiation often depends on biopsy

#### General Considerations

Squamous cell carcinoma or adenocarcinoma of the esophagus is common in old men The lower and middle portions of the esophagus are most often involved

#### Clinical Findings

**A Symptoms and Signs** Vague discomfort and strange sensations in swallowing may precede more definite symptoms by months In the classic syndrome progressive dysphagia begins with sticking of large particles particularly with rapid eating and progresses to inability to swallow even liquids Pain and sensation of a lump may occur and at times are at the same level as the lesion Regurgitation belching hoarseness and cough occur late when obstruction is nearly complete Weight loss to extreme emaciation is usual

**B X ray findings** X ray shows an irregular or annular obstruction

**C Esophagoscopy** study and biopsy or lavage and cytologic study is necessary to prove the diagnosis

#### Treatment & Prognosis

There is no satisfactory treatment for esophageal carcinoma Soft or liquid food should be given as tolerated gastrostomy feedings may be given in selected cases

Surgical removal is reserved for the few patients who have no demonstrable metastases and are good surgical risks Deep radiation therapy may be employed in selected cases when surgery is not feasible

In advanced cases dilatation may be palliative for short periods

Buschke F Surgical and radiological results in the treatment of esophageal carcinoma Am J Roentgenol 71 9 21 1954  
Marshak R H Roentgen findings in benign and malignant tumors of the esophagus J Mt Sinai Hosp 23 75 80 1956  
Nightingale E J & others Some important clinical aspects of esophageal carcinoma an analysis of 413 cases Am J Digest Dis 21 341 53 1954

### DISEASES OF THE STOMACH

#### ACUTE SIMPLE GASTRITIS

Acute gastritis probably the most common disturbance of the stomach is frequently accompanied by generalized enteritis It occurs in all age groups The causes are as follows (1) chemical irritants e g alcohol

(2) bacterial infections or toxins, e. g., staphylococcal food poisoning, scarlet fever, pneumonia, (3) viral infections, e. g., "viral gastroenteritis," measles, hepatitis, influenza; and (4) allergy, e. g., to shellfish.

#### Clinical Findings.

**A. Symptoms and Signs** Anorexia is always present and may be the only symptom. More commonly there is epigastric fullness and pressure, nausea, and vomiting. Hematemesis occurs occasionally but is rarely severe. Diarrhea and cramping pain (enteritis), malaise, chills, headache, and muscle cramps may be present. The patient may be prostrated and dehydrated. Examination shows mild epigastric tenderness.

**B. Laboratory Findings** Mild leukocytosis may be present.

**C. Gastroscopy** is rarely performed but shows diffuse erythema, occasional petechiae, and copious adherent mucus.

#### Treatment & Prognosis.

Give nothing by mouth until acute symptoms of pain and nausea have subsided. Then give clear liquids and progress to a soft bland diet as tolerated. Sedatives, phenothiazine tranquilizers, or opiates may be used as indicated. Symptoms last 1-7 days.

### ACUTE CORROSIVE GASTRITIS

Ingestion of corrosive substances is most common in children but may occur in attempted suicide. The substances most commonly swallowed are strong acids (sulfuric, nitric), alkalis (lye, potash), oxalic acid, iodine, bichloride of mercury, arsenic, silver nitrate, and carbolic acid. Gastric changes vary from superficial edema and hyperemia, deep necrosis and sloughing, to perforation.

Corrosion of the lips, tongue, mouth, and pharynx, and pain and dysphagia due to esophageal lesions are usually present. Nitric acid causes brown discoloration, oxalic acid causes white discoloration of mucous membranes. There is severe epigastric burning and cramping pain, nausea and vomiting, and diarrhea. The vomitus is often blood-tinged. Severe prostration with a shock-like picture and thirst may occur. Palpation of the abdomen may show epigastric tenderness or extreme rigidity.

Leukocytosis and proteinuria are present. X-ray examination may show strictures.

Immediate treatment consists of prompt administration of the appropriate antidote. Avoid emetics and lavage if corrosion is severe because of the danger of perforation. Treat gastritis as for acute simple gastritis.

After the acute phase has passed, place the patient on a peptic ulcer regimen. If perforation has not occurred, recovery is the rule. However, pyloric stenosis may occur early or late, requiring gastric aspiration, parenteral fluid therapy, and surgical repair.

The amount of the corrosive substance, its local and general effects, and the speed with which it is removed or neutralized determine the outcome. If the patient survives the acute phase, gastric effects are usually overshadowed by esophageal strictures, although chronic gastritis or stricture formation at the pylorus may follow.

### CHRONIC GASTRITIS

#### Essentials of Diagnosis

- Long-standing upper abdominal dyspeptic symptoms
- Mild epigastric tenderness or no physical findings whatever
- X-ray may show heavy mucosal folds.
- Gastroscopic appearance makes the diagnosis

Since clinical and pathologic findings correlate so poorly, the diagnosis of chronic gastritis should be made only on the basis of anatomic findings obtained via gastric biopsy, surgery, or autopsy. The differential diagnosis includes other chronic upper abdominal disorders such as peptic ulcer, hiatus hernia, esophagitis, and pancreatic disease.

#### General Considerations.

Chronic gastritis is usually classified (on the basis of gastroscopic observation) as (1) chronic superficial gastritis, with hyperemia, edema, hemorrhages, and superficial erosions, (2) atrophic gastritis, with thin, pale mucosa, narrow gastric folds (in the hyperplastic form of atrophic gastritis, fine orange nodules), and (3) chronic hypertrophic gastritis, with thick, dull, velvety mucosa in large folds and cobblestone nodularity between folds. The cause is not known. Even in those types which are secondary to tumors, ulcers, or obstruction or which occur after surgery, the degree and extent of the process may not

correlate well with the severity of the inciting factors. Other causative factors are long-standing irritation, acute gastritis, allergy, disturbances of circulation, deficiency states, and psychic disorders.

### Clinical Findings

**A Symptoms and Signs** Gastrointestinal symptoms, if they occur, may include anorexia, epigastric pressure and fullness, heartburn, nausea, vomiting, specific food intolerance, peptic ulcer-like syndrome, and anemia or gross hemorrhage.

Physical findings are often absent or consist only of mild epigastric tenderness.

**B Laboratory Findings** The laboratory findings may be entirely normal. The gastric analysis, although not diagnostic, frequently shows achlorhydria with atrophic gastritis and hypersecretion with chronic hypertrophic gastritis.

**C X-ray Findings** The x-ray in chronic hypertrophic gastritis may show heavy folds and increased motility.

### Treatment & Prognosis

The treatment of chronic gastritis, except in those cases associated with pernicious anemia or iron-deficiency anemia, is not very successful. However, the use of a peptic ulcer regimen, combined with the elimination of aggravating factors such as alcohol, may reduce the severity of the symptoms.

Atkins, L., & E. B. Benedict. Correlation of gross gastroscopic findings with gastroscopic biopsy in gastritis. *New England J Med* 254 641-4, 1956.

Palmer, E. D. Gastritis, a re-evaluation. *Medicine* 33 189-290, 1954.

## PEPTIC ULCER

A peptic ulcer is an acute or chronic benign ulceration occurring in a portion of the digestive tract which is accessible to gastric secretions. Since an active peptic ulcer does not occur in the absence of acid-peptic gastric secretions, peptic ulcers are not found in conditions where acid is absent.

Other factors in peptic ulceration (besides the presence of gastric acidity) include hypersecretion and decreased tissue resistance.

Kirsner, J. B., Kassriel, R. S., & W. L. Palmer. Peptic ulcer; review of recent literature pertaining to etiology, pathogenesis and certain clinical aspects. *Advances Int Med* 8 41-124, 1956.

Mirsky, I. A. Physiologic, psychologic and social determinants in the etiology of duodenal ulcer. *Am J Digest Dis (New Series)* 3 285-314, 1958.

## I DUODENAL ULCER

### Essentials of Diagnosis

- Epigastric distress 45-60 minutes after meals and relieved by food, antacids, or vomiting.
- Epigastric tenderness and guarding.
- Chronic and periodic symptoms.
- Free gastric acid and gastric hypersecretion.
- Ulcer crater or deformity of duodenal bulb on x-ray.

When symptoms are typical the diagnosis of peptic ulceration can be made with assurance, when the symptoms are atypical, duodenal ulcer may be confused clinically with functional gastrointestinal disease, gastritis, gastric carcinoma, and irritable colon syndrome. Final diagnosis often depends upon x-ray.

### General Considerations.

Duodenal ulcer occurs in about 10% of people at some time. Although the average age at onset is 33 years, duodenal ulcer may occur at any time from infancy to the later years. It is 4 times as common in males as in females. Occurrence during pregnancy is unusual.

Duodenal ulcer is 4 or 5 times as common as benign gastric ulcer. Morbidity due to peptic ulcer is a major public health problem.

About 95% of duodenal ulcers occur in the duodenal bulb or cap, i.e., the first 5 cm (2 inches) of the duodenum. The remainder are between this area and the ampulla. Ulcers below the ampulla are rare. The majority are near the lesser curvature. The ulceration varies from a few mm to 1-2 cm. (3/8-3/4 inch) in diameter and extends at least through the muscularis mucosa, often through to the serosa and into the pancreas. The margins are sharp, but the surrounding mucosa is often inflamed and edematous. The base consists of granulation tissue and fibrous tissue representing healing and fibrinoid necrosis.

### Clinical Findings

**A Symptoms and Signs** Symptoms may be absent or vague and atypical. In the typical case pain is described as gnawing, burning, cramp-like, or aching, or as "heartburn", it is usually mild to moderate, located over a small area near the midline in the epigastrium near the xiphoid. The pain may radiate below the costal margins, into the back, or, rarely, to the right shoulder. Nausea may be present, and vomiting of small quantities of highly acid gastric juice with little or no retained food may occur. The distress usually occurs 45-60 minutes after a meal, is usually absent before breakfast, worsens as the day progresses, and may be most severe between 12 midnight and 2 00 a.m. It is relieved by food, milk, alkalies, and vomiting generally within 5-30 minutes.

Remissions often occur, followed by exacerbations precipitated by stress, infection, or emotional strain.

Signs are usually limited to tenderness in the epigastrium, superficial as well as deep (75% of cases), and voluntary epigastric muscle guarding.

**B Laboratory Findings** Bleeding, hypochromic anemia, and occult blood in the stools occur in chronic ulcers. Gastric analysis shows acid in all cases and hypersecretion in most cases.

**C X-ray Findings** An ulcer crater is demonstrable by x-ray in 50-70% of cases but may be obscured by cicatricial distortion of the duodenal cap. When no ulcer is demonstrated the following are suggestive of ulceration: (1) Irritability of the bulb with difficulty in retaining barium there, (2) point tenderness over the bulb, (3) pylorospasm, (4) gastric hyperperistalsis, (5) hypersecretion or retained secretions, and (6) large gastric rugae.

### Complications

**A Intractability to Treatment** Most cases of apparently intractable ulcer are probably due to an inadequate medical regimen or failure of cooperation on the part of the patient. The designation "intractable" should be reserved only for those patients who have received an adequate supervised trial of therapy. The possibility of complications of the ulcer must always be considered.

**B Hemorrhage Due to Peptic Ulcer** Hemorrhage is caused either by erosion of an ulcer into an artery or vein or, more commonly, by bleeding from granulation tissue. The majority of bleeding ulcers are on the posterior

wall. The sudden onset of weakness, faintness, dizziness, chilliness, thirst, cold moist skin, desire to defecate, and the passage of loose tarry or even red stools with or without coffee-ground vomitus is characteristic of acute gastrointestinal hemorrhage.

The blood findings lag behind the blood loss by several hours and may give a false impression of the quantity of blood lost.

**C Perforation** It occurs almost exclusively in males between the ages of 25 and 40. The symptoms and signs are those of peritoneal irritation and peritonitis, ulcers which perforate into the lesser peritoneal cavity cause less dramatic symptoms and signs. A typical description of perforated peptic ulcer is an acute onset of epigastric pain, often radiating to the shoulder or right lower quadrant and sometimes associated with nausea and vomiting, followed by a lessening of pain for a few hours, and then by board-like rigidity of the abdomen, fever, rebound tenderness, absent bowel sounds, leukocytosis, tachycardia, and even signs of marked prostration. X-ray demonstration of free air in the peritoneal cavity confirms the diagnosis.

Perforation may be acute, subacute, or chronic.

**D Penetration** Extension of the crater beyond the duodenal wall into contiguous structures without extension into the free peritoneal space occurs fairly frequently with duodenal ulcer and is one of the important causes of failure of medical treatment. Penetration generally occurs in ulcers on the posterior wall and extension is usually into the pancreas, but the liver, biliary tract, or gastrohepatic omentum may be involved.

Radiation of pain into the back, night distress, inadequate or no relief from eating food or taking alkalies and, in occasional cases, relief upon spinal flexion and aggravation upon hyperextension - any or all of these findings in a patient with a long history of duodenal ulcer usually signify penetration.

**E Obstruction.** Minor degrees of pyloric obstruction are present in about 20-25% of patients with duodenal ulcer, but clinically significant obstruction is much less common. The obstruction is generally caused by edema and spasm associated with an active ulcer, but it may occur as a result of scar tissue contraction even in the presence of a healed ulcer.

The occurrence of epigastric fullness or heaviness and, finally, copious vomiting after meals - with the vomitus containing undigested food from a previous meal - suggest obstruction.

The diagnosis is confirmed by the presence of an overnight gastric residual of greater than 50 ml containing undigested food, and x-ray evidence of obstruction, gastric dilatation, and hyperperistalsis. A succussion splash on pressure in the left upper quadrant may be present, and gastric peristalsis may be visible.

#### Treatment.

##### A Acute Phase

1 General Measures - The patient should have 2 or 3 weeks rest from work if possible. If the home situation is unsatisfactory or if the patient is uncooperative, hospitalization is recommended. If the patient must continue to work, he should be given careful instructions about the medical program. Arrangements should be made for rest periods and sufficient sleep. Anxiety should be relieved whenever possible, but active psychotherapy during the acute phase is usually not indicated.

Alcohol should be strictly forbidden. If the patient can quit smoking without too much distress, he should do so.

The following drugs may aggravate peptic ulcer or may even cause perforation and hemorrhage: corticotropin, the adrenal steroids, rauwolfia, phenylbutazone, and large doses of salicylates. They should be discontinued.

2 Diet - Numerous dietary regimens have been designed for the patient with peptic ulcer. The important principles in the dietary management of peptic ulcer are as follows: (1) Nutritious bland diet, (2) frequent small feedings, (3) regularity of meals, (4) restriction of foods and beverages which stimulate gastric secretion, especially alcohol and coffee.

Avoid "short-cuts." In general most of the short-cut or "modified" regimens do not save time and in many cases they not only fail to relieve symptoms but actually prolong convalescence.

Boiled cow's milk, protein preparations, or goat's milk may be given to patients who are sensitive to cow's milk. Skimmed milk may be substituted if the patient is obese.

Restrictions - Meat extracts, bran, raw vegetables and fruits, fried foods, condiments, spices, alcohol, coffee, tea, and all very hot very cold, and carbonated beverages.

3 Antacids - Many antacids are available, and in certain circumstances each of the agents listed below enjoys special advantages. Caution: All patients on antacid therapy should be watched for diarrhea, constipation, and fecal impaction.

In order to be effective, antacids must be taken frequently. During the acute phase they must be taken every hour or half-hour during the day and night if necessary. As improve-

ment progresses the patient may increase the interval between doses to 2 hours. The drugs should be taken on a regular program, irregular and p.r.n. antacid therapy is not effective.

#### (1)

R Magnesium oxide	30-60.0 (1-2 oz)
Calcium carbonate,	
q s ad	120.0 (4 oz)

Sig Take 1/2-1 tsp in one-half glass of water as directed

Magnesium oxide is a laxative drug and calcium carbonate tends to produce constipation. By varying the amount of magnesium oxide in this prescription, the laxative or constipating effects of the 2 ingredients may be effectively balanced. The powder may be given in alternating doses with aluminum hydroxide gels.

#### (2)

R Magnesium oxide	20-60.0 (2/3-2 oz)
Bismuth subcarbonate	20.0 (2/3 oz)
Calcium carbonate,	
q s ad	120.0 (4 oz)

Sig 1/2-1 tsp in one-half glass of water as directed

(3) Magnesium trisilicate, 1/2-1 tsp in one-half glass of water as directed

(4) Aluminum hydroxide gel - These agents have enjoyed popular use because they are convenient to administer, do not tend to cause alkalosis and have local adsorbent and demulcent actions. However, they are constipating. Interfere with phosphate and vitamin absorption, may have to be given in large doses, and occasionally fail to give relief. Give aluminum hydroxide gel (Amphojel<sup>®</sup>) (liquid), 1-2 tsp in one-half glass of water every 1-4 hours, or aluminum hydroxide gel (dried tablets), 1-2 tablets chewed and followed with one-half glass of water every 1-4 hours, or aluminum hydroxide gel (dried)-magnesium trisilicate tablets (Gel-usil<sup>®</sup>), 1-2 tablets chewed every 2-4 hours and followed with one-half glass of water, or aluminum hydroxide gel-magnesium trisilicate mixtures (liquid), 1-2 tsp in one-half glass of water every 1-4 hours (less constipating). The addition of magnesium trisilicate increases the neutralizing power and protective coating action of the aluminum hydroxide gel. Aluminum hydroxide and magnesium hydroxide colloidal suspension, or tablets (Aludrox<sup>®</sup>, Maalox<sup>®</sup>).

is another useful nonconstipating antacid mixture which is given in doses comparable to those of other aluminum hydroxide preparations

4 Sedatives - Tense and apprehensive patients will usually profit greatly from sedation. The barbiturates are preferred, alone or in combination with antispasmodic drugs. Hypnotic doses of the barbiturates may be necessary to ensure sleep.

5 Belladonna preparations, when employed in proper dosage, are probably as effective as any of the anticholinergic preparations and have the added advantage of being inexpensive.

(1) Belladonna tincture, 0.3-0.6 ml (5-10 drops) in one-half glass of water t i d, 20-30 minutes before meals and at bedtime as necessary (0.6 ml of the tincture equals about 0.2 mg of atropine). This preparation permits rather delicate "titration" of desired antispasmodic effect by simply regulating the number of drops, but is a nuisance to the patient to measure each time.

(2) Belladonna extract, 8-15 mg ( $\frac{1}{8}$ - $\frac{1}{4}$  gr) t i d, 20-30 minutes before meals and at bedtime (15 mg equals about 0.2 mg atropine alkaloid).

(3)

R Belladonna tincture 10-30 0 ( $\frac{1}{3}$ -1 oz)  
Elixir of phenobarbital, q s ad 120 0 (4 oz)

Sig One tsp in one-half glass of water t i d, 20-30 minutes before meals and at bedtime as necessary

(4)

R Belladonna extract 8-15 mg ( $\frac{1}{8}$ - $\frac{1}{4}$  gr)  
Phenobarbital 15 mg ( $\frac{1}{4}$  gr)

Sig One tablet t i d, 20-30 minutes before meals and at bedtime as necessary

6 Anticholinergic-antispasmodic drugs - These drugs should generally be given 3-4 times daily in dosages large enough to produce oral dryness, blurred vision, tachycardia, urinary retention, and other atropine-like side effects may occur due to blockage of parasympathetic activity. These atropine substitutes are, however, quaternary amines and do not cause CNS side effects. Examples of these drugs (together with an initial dose which can be given q i d and increased until side effects appear) are as follows: Diphenhydramine methylsulfate (Prantal<sup>®</sup>), 100 mg; hexocyclium methylsulfate (Tral<sup>®</sup>) 25 mg; homatropine methyl-

bromide, 5 mg; isopropamide iodide (Darbid<sup>®</sup>), 5 mg (b i d only); mepenzolate bromide (Banthine<sup>®</sup>), 25 mg; methantheline bromide (Banthine<sup>®</sup>), 50 mg; methscopolamine bromide (Pamne<sup>®</sup>) 2.5 mg; oxyphenonium bromide (Antrenyl<sup>®</sup>), 5 mg; penthenate bromide (Monodral<sup>®</sup>), 5 mg; pipenzolate methylbromide (Piptal<sup>®</sup>), 5 mg; propantheline bromide (Pro-Banthine<sup>®</sup>) 15 mg; tridihexethyl chloride (Pathlon<sup>®</sup>), 25 mg.

## B Convalescent Phase

1. Re-examination - When clinical quiescence of the lesion is evident (based on freedom from symptoms) a repeat gastrointestinal x-ray series is advisable to determine whether or not there is x-ray evidence of healing. In gastric lesions, failure of clinical improvement and x-ray improvement of the ulcer crater within a period of 3-4 weeks on a careful medical regimen is suggestive of gastric malignancy.

2. Education of patient regarding recurrences - The chronic and recurrent nature of the illness should be explained to the patient, and he should be warned about the complications of careless or improper treatment. It should be emphasized that the following factors are most frequently responsible for recurrence of ulcer: Improper diet and irregular eating habits; irregular living habits (long or irregular hours); use of alcohol or tobacco; emotional stress and infections, particularly of the upper respiratory tract. The patient should be instructed to return to the ulcer regimen or a modification of it if symptoms recur or if he recognizes that he is exposing himself to conditions known to aggravate the ulcer. In addition to diet information, antacid and other medications should be readily available.

3. Rest and recreation - Provisions should be made for rest and recreation to promote physical and mental relaxation.

## C Treatment of Complications

### 1. Hemorrhage -

(1) Institute immediate emergency measures for treatment of hemorrhage and shock (see p. 2). Hospitalize the patient at absolute bed rest and keep him comfortably warm. If sedation is necessary, give one of the following: codeine phosphate, 30-65 mg ( $\frac{1}{2}$ -1 gr.) subcut or orally; dihydromorphine (Dilaudid<sup>®</sup>), 4 mg ( $\frac{1}{16}$  gr.) subcut every 4-6 hours p r n, or sodium phenobarbital, 0.03-0.1 Gm ( $\frac{1}{2}$ -1  $\frac{1}{2}$  gr.) subcut or orally p r n during the first 24-48 hours. Phenobarbital may be continued for several days if necessary. Avoid morphine, if possible, since it may cause nausea and predispose to shock.

. Blood should be given to restore effective blood volume and maintain BP and pulse. In severe hemorrhage the time, rate, and volume of blood administration should suit the physiologic needs, and large amounts of blood may be given when indicated. Transfusions must be given if hemorrhage is severe (hemoglobin < 8 Gm/100 ml or RBC < 2.5 million), if immediate surgery is contemplated, or if symptoms of anoxia or shock are not rapidly controlled.

Observe pulse, respirations, and BP every 30-60 minutes since these data may give information regarding shock status in advance of blood changes. Observe all vomitus and stools for gross or occult blood. Type and cross-match the patient's blood carefully as soon as possible. Have whole blood or plasma available without delay if blood or plasma is not available, saline or plasma expander may temporarily maintain intravascular volume until blood can be obtained. Take a complete blood count and determine hematocrit initially and serially as indicated. Determine blood NPN or urea nitrogen for comparison with later studies as an indication of blood in the gastrointestinal tract.

(2) General measures - Correct dehydration and salt depletion with physiologic saline solution, 1-1.5 L daily I.V., and oral liquid feedings as soon as tolerated (see below). Sodium chloride 3-6 Gm/L, may be added to the liquid food mixture to prevent salt depletion.

The policy of initial starvation is a matter of considerable controversy. Since the patient is often nauseated and anorexic, or even in shock on the first day, food may be safely withheld. If the patient is nauseated or vomiting, thirst may be controlled by fluids given parenterally. The patient may be permitted to dissolve ice chips or hard fruit-flavored candy under the tongue to relieve thirst. If the patient is hungry and is not vomiting, begin immediate administration of bland foods. It is best to begin with a liquid diet of hourly feedings of milk and cream mixture, with supplementary antacid powders. Solid bland foods may be added when the patient has shown apparent clinical improvement on the milk and cream regimen within 1-2 weeks and when the stools have shown no occult blood for 2-3 days. A more liberal approach (e.g., Meutengracht) permits immediate feeding of all nonirritant, high-caloric foods, but in puréed form.

(3) Convalescent care - After the acute episode the conservative medical regimen outlined for uncomplicated peptic ulcer should be instituted.

(4) Surgery should be considered if hemorrhage persists and the patient's condition does not stabilize with 2-4 L. of blood. As soon as the patient's condition permits, a gastrointestinal x-ray series should be performed to help localize the source or identify the character of the bleeding lesion. Manipulation during such examinations should be as gentle as possible.

2. Perforation - Acute perforation constitutes a medical emergency. Immediate surgical repair, preferably by simple surgical closure, is indicated. More extensive operations are usually unwise at the time of the acute episode because of the increased operative hazard due to the patient's poor physical condition. If the patient has been receiving corticotropin (ACTH) or cortisones, these drugs must be discontinued. If the patient has had no previous therapy or if previous therapy has been inadequate, he may then be placed upon a conservative medical regimen. If the patient has had an adequate trial of therapy, prepare him for possible further extensive operative procedures by transfusions and other supportive measures. The treatment of subacute or chronic perforation may be medical or surgical, depending upon the presence or absence of complications (e.g., abscess, involvement of neighboring viscera) or the persistence and severity of symptoms.

The morbidity and mortality depend upon the amount of spillage and especially the time lapse between perforation and surgery. The danger increases abruptly after a delay of 12-24 hours.

3. Obstruction - Obstruction due to spasm and edema can usually be treated adequately by gastric decompression and ulcer therapy; obstruction due to scar formation requires surgery. It must be remembered that the obstruction may not represent a complication of an ulcer but may be due to a primary neoplastic disease, especially in those patients with no history or only a short history of peptic ulcer.

(1) Medical measures (for obstruction due to spasm or edema) consist of bed rest, preferably in a hospital, continuous gastric suction for 48 hours, and parenteral administration of electrolytes and fluids. After 48 hours begin hourly feedings of 30 ml of milk. Aspire gastric juice every 12 hours to measure gastric residual. Do not use anticholinergic drugs since they delay gastric emptying. Give sedative or sedative-tranquillizer drugs, and a progressive Sippy diet as tolerated. Antacids may be employed as for treatment of uncomplicated ulcer.



(2) Surgical measures (for obstruction due to scarring) are indicated only after a thorough trial of conservative measures. Various procedures have been recommended. It is currently the practice to perform gastric resection in most cases, or antrectomy and vagotomy.

#### Prognosis.

Duodenal ulcer tends to have a chronic course with remissions and exacerbations. Many patients can be adequately controlled by medical management. About 25% develop complications, and 5-10% ultimately require surgery.

Brooks, J.R., & F.D. Moore: Duodenal ulcer: the present status of definitive surgery, the selection and management of patients undergoing operation. *New England J Med* 260 1019-24, 1069-76, and 1124-30, 1959.

Byrne, J.J.: Treatment of perforated peptic ulcer. *New England J. Med* 266, 1265-8, 1962.

Kirsner, J.B., & W.L. Palmer: Treatment of peptic ulcer. Current concepts. *Am J Med* 29:793-803, 1960.

Marshall, E.A., Sass, M.D., & H. Brown: Medical management of obstructive complications. *Surg. Gynec. & Obst.* 102:33-7, 1956.

Wirts, C.W., & T. Bodi: Management of hemorrhaging gastroduodenal ulcer. *J.A.M.A.* 163:1229-34, 1957.

## 2. GASTRIC ULCER

#### Essentials of Diagnosis

- Epigastric distress on an empty stomach, relieved by food, alkalies, or vomiting.
- Epigastric tenderness and voluntary muscle guarding
- Anemia, occult blood in stool, free gastric acid.
- Ulcer demonstrated by x-ray or gastroscopically.

Most important is the differentiation of benign gastric ulcer from malignant gastric ulcer. The symptoms of gastric ulcer, especially if atypical, need differentiation from those of irritable colon, gastritis, and functional gastrointestinal distress.

#### General Considerations.

Benign gastric ulcer is in many respects similar to duodenal ulcer. Acid gastric juice is necessary for its production, but decreased tissue resistance appears to play a more important role than hypersecretion.

About 60% of benign gastric ulcers are found within 6 cm (2 3/8 inches) of the pylorus. The ulcers are generally located at or near the lesser curvature and most frequently on the posterior wall. Another 25% of the ulcers are located higher on the lesser curvature.

Gastric ulcers are 2 or 3 times more common in males, usually over 40 years of age.

#### Clinical Findings.

**A. Symptoms and Signs.** There may be no symptoms or only vague and atypical symptoms. Typically the epigastric distress is described as gnawing, burning, aching, or "hunger pangs" referred at times to the left subcostal area. Episodes occur usually 45-60 minutes after a meal and are relieved by food, alkalies, or vomiting. Nausea and vomiting are frequent complaints. There may be a history of remissions, with exacerbations occurring in the winter months. Weight loss, constipation, and fatigue are common.

Epigastric tenderness or voluntary muscle guarding is usually the only finding.

**B. Laboratory Findings.** If bleeding has occurred, there may be hypochromic anemia or occult blood in the stool. The gastric analysis always shows free hydrochloric acid after histamine and the presence of low normal to normal secretion.

**C. X-rays or gastroscopic examination** usually confirm the presence of an ulcer.

#### Complications

Hemorrhage, perforation, and obstruction may occur (see Complications of Duodenal Ulcer).

#### Differential Diagnosis.

A favorable response to hospital management is presumptive evidence that the lesion is benign and not malignant. Malignant ulcers may respond initially, but residual changes at the site usually demonstrate the true nature of the process.

#### Treatment.

Since about 10% of gastric ulcers prove to be due to carcinoma, ulcer treatment (as for duodenal ulcer) should be intensive, and failure to respond in 3-4 weeks with complete healing

should be regarded as an indication for surgical exploration and resection. However, even a carcinoma may show improvement on an ulcer regimen, and clinical relief does not mean that the ulcer is benign. Repeated follow-up at 6 weeks, 3 months, and 6 months after apparently complete healing is therefore indicated. In the event of recurrence under intensive medical management, perforation, obstruction, or massive uncontrollable hemorrhage, surgery is mandatory.

### Prognosis.

Gastric ulcers have a lesser tendency to recur than duodenal ulcers. There is no significant evidence that malignant degeneration of gastric peptic ulceration ever occurs.

Kirsner, J B., Clayman, C B., & W L Palmer: The problem of gastric ulcer. Arch Int Med 104 995-1020, 1959

## 3. STOMAL (MARGINAL) ULCER

Marginal ulcer should be suspected when there is a history of operation for an ulcer followed by recurrence of abdominal symptoms after a symptom-free interval of months to years. The marginal ulcer incidence after simple gastroenterostomy is 35-75%, after subtotal gastrectomy or vagotomy, about 5%. Approximately half of the ulcers are jejunal, and the others are located on the gastric side of the anastomosis. The abdominal pain is burning or gnawing, often more severe than the preoperative ulcer pain, and is located lower in the epigastrium, even below the umbilicus and often to the left. The pain often covers a wider area and may radiate to the back.

The "food-pain rhythm" of peptic ulcer distress frequently occurs earlier (within an hour) in marginal ulcer as a result of more rapid emptying time, and relief with antacids, food, and milk may be incomplete and of short duration. Nausea, vomiting, and weight loss are common. Hematemesis occurs frequently. Low epigastric tenderness with voluntary muscle guarding is usually present. An inflammatory mass may be palpated. Anemia and occult blood in the stool are common. On gastric analysis free hydrochloric acid can be demonstrated, although rapid emptying makes the procedure difficult. On x-ray the ulcer niche at the stoma is often difficult to demonstrate, although compression films are helpful and narrowing of the stoma is suggested. On gastroscopy the marginal ulcer may be

visualized, jejunal craters can also be seen occasionally.

Stomal ulcer must be differentiated from functional gastrointestinal distress, especially in a patient concerned about the possibility of recurrence of an ulcer after surgery. Atypical symptoms must be differentiated from gastritis and pancreatic disease.

Complications include gross hemorrhage, perforation, stenosis of the stoma, and gastro-jejunal fistula.

A course of ulcer therapy should be given as outlined for duodenal ulcer. Stomal ulcers are often resistant to medical therapy, however, and vagotomy or a more extensive gastrectomy is usually necessary to decrease the acid secretion of the stomach.

## POSTGASTRECTOMY (DUMPING) SYNDROME

The postgastrectomy (dumping) syndrome probably occurs in about 10% of patients after partial gastrectomy. Its cause is not completely understood, but most evidence points to the following sequence of events. The ingestion and rapid hydrolysis of food, especially carbohydrates, results in hypertonicity in the jejunal contents, this causes a rapid inflow of fluid into the jejunum from the surrounding plasma and extracellular tissues, creating a drop in the circulating blood volume. This change in blood volume produces a sympathetic vasomotor response, i.e., the symptoms the patient complains of. This sympathetic response although possibly due in part to a distended jejunum, is mainly secondary to the diminished blood volume.

One or more of the following symptoms occur within 20 minutes after meals: sweating, tachycardia, pallor, epigastric fullness and grumbling, warmth, nausea, abdominal cramps, weakness, and, in severe cases, syncope, vomiting, or diarrhea. Nonspecific ECG changes may be noted. Blood sugar is not low during an attack.

It is important to distinguish this syndrome from the much rarer spontaneous hypoglycemia which occurs in some postgastrectomy patients and is associated with a low blood sugar. This latter syndrome occurs much later after the meal (1-3 hours) and is relieved by the ingestion of food.

Changing the diet to frequent small, equal feedings high in protein, moderately high in fat, and low in carbohydrate usually reduces the severity of symptoms. Sedative and anticholinergic drugs may be of value.

Fisher, J A Taylor W, & J A Cannon

The dumping syndrome correlations between its experimental production and clinical incidence Surg Gynec & Obst 100 559 65 1955

Machella T E Undesirable sequelae of subtotal gastric resection M Clin North America 40 391-402 1956

## CARCINOMA OF THE STOMACH

### Essentials of Diagnosis

- Upper gastrointestinal symptoms with weight loss in patients over age 40
- Palpable abdominal mass
- Anemia occult blood in stools positive cytology
- Gastroscopic and x-ray abnormality

The symptoms of carcinoma of the stomach are often mistaken for those of benign gastric ulcer chronic gastritis irritable colon syndrome or functional gastrointestinal disturbance x-ray and gastroscopic findings must be differentiated from those of benign gastric ulcer or tumor In case of doubt an exploratory operation is in order

It often is impossible to distinguish gastric carcinoma from gastric sarcoma on clinical grounds alone

### General Considerations

Carcinoma of the stomach is the most frequent cancer of the digestive tract and causes about 20% of all cancer deaths It occurs predominantly in males over 40 years of age Delay of diagnosis is caused by absence of definite early symptoms and by the fact that patients treat themselves instead of seeking early medical advice Further delays are due to the equivocal nature of early findings and to temporary improvement with symptomatic therapy

A history of the following precancerous or possibly precancerous conditions should alert the physician to the danger of stomach cancer

- (1) Benign adenomas Reported incidences of malignant change vary from 12 to 80%
- (2) Atrophic gastritis of pernicious anemia The incidence of adenomas and carcinomas is significantly increased
- (3) Chronic gastritis particularly atrophic gastritis There is a wide variation in the reported incidence of gastritis with cancer and a definite relationship has not been proved

(4) Gastric ulcer The major problem is in the differentiation between benign and malignant ulcer

(5) Achlorhydria The incidence of lowered secretory potential in early life is higher in those patients who later develop carcinoma

Carcinoma may originate anywhere in the stomach Grossly lesions tend to be of 4 types (Boremann)

- Type I Polypoid intraluminal mass
- Type II Noninfiltrating ulcer
- Type III Infiltrating ulcer
- Type IV Diffuse infiltrating process (to linitis plastica)

*Gross typing generally correlates better with prognosis than the histologic grading of malignancy i e type I has a better prognosis than type II etc*

### Clinical Findings

**A Symptoms and Signs** There is no characteristic symptom or symptom complex in early gastric carcinoma The patient may complain of vague fullness nausea sensations of pressure belching and heartburn after meals with or without anorexia especially for meat These symptoms in association with weight loss and decline in general health and strength in a man over 40 years of age should suggest the possibility of stomach cancer Diarrhea hematemesis and melena may be present

Specific symptom complexes may be determined in part by the location of the tumor A peptic ulcer-like syndrome generally occurs with ulcerated lesions (types II and III) and in the presence of acid secretion but may occur with complete achlorhydria Unfortunately symptomatic relief with antacids (even healing of the ulcer) tends to delay diagnosis Symptoms of pyloric obstruction are progressive postprandial fullness to retention type vomiting of almost all foods Lower esophageal obstruction causes progressive dysphagia and regurgitation

Physical findings are usually limited to weight loss and if anemia is present pallor In about 20% of cases a palpable abdominal mass is present this does not necessarily mean that the lesion is inoperable Liver or peripheral metastases may also be present

**B Laboratory Findings** About 65% of patients have achlorhydria and 25% have normal or hypersecretion If bleeding occurs there will be occult blood in the stool and mild to severe anemia With bone marrow invasion the anemia may be normoblastic

C X-ray or gastroscopic visualization of the lesion is the most important diagnostic finding. Positive cytologic examination of exfoliated cells is diagnostic, but false-negatives occur frequently.

#### Differential Diagnosis

Stomach sarcoma is often clinically indistinguishable from gastric carcinoma until biopsy examination. Primary sarcoma of the stomach is rare but it accounts for 10% of malignant gastric tumors in persons under 30 years of age. A palpable mass is more frequent in sarcomatous lesions than in gastric carcinoma, and the x-ray picture is characteristically that of a well circumscribed intramural mass with frequently a central crater.

It is important to differentiate localized sarcomatous lesions from gastric lymphomas which are better treated by irradiation than resection. The prognosis varies widely with the histologic type but in general is better than that of gastric carcinoma.

#### Treatment

Surgical resection is the only curative treatment. Signs of metastatic disease include a hard nodular liver, enlarged left supraclavicular (Virchow's) nodes, skin nodules, ascites, resectal shelf, and x-ray evidence of osseous or pulmonary metastasis. If none of these are present and there is no other contraindication to operation, exploration is indicated. The presence of an abdominal mass is not a contraindication to laparotomy, since bulky lesions can often be totally excised. Palliative resection or gastroenterostomy is occasionally helpful in pyloric obstruction. X-ray therapy is of no value.

#### Prognosis

There is wide variation in the biologic malignancy of gastric carcinomas. In many the disease is widespread before symptoms are apparent. In a fortunate few a slow growth may progress over years and be resectable even at a late date. The operative mortality in partial gastrectomy for cancer is about 5% with a 27% five-year survival rate; for total gastrectomy, the mortality is about 9% with a 14% five-year survival rate.

Flood C A. Carcinoma of the stomach. *Ann Int Med* 48:919-55, 1958.

## BENIGN TUMORS OF THE STOMACH

Most benign tumors do not cause symptoms, and often are so small that they are overlooked on x-ray examination. Their importance lies in the problem of differentiation from malignant lesions, their precancerous possibilities, and the fact that they occasionally cause symptoms.

These tumors may be of epithelial origin (e.g., adenomas, papillomas) or mesenchymal origin (e.g., leiomyomas, fibromas, hemangiomas, lipomas, hemangiomas). Adenomas are reported to undergo malignant change in 12-80% of cases, the mesenchymal tumors which are intramural rarely undergo malignant change.

**A Symptoms and Signs.** Large tumors may cause a vague feeling of epigastric fullness or heaviness. Tumors located near the cardia or pylorus may produce symptoms of obstruction. If bleeding occurs it will cause symptoms and signs of acute gastrointestinal hemorrhage (e.g., tarry stools, syncope, a sweating, vomiting of blood). Chronic blood loss will cause symptoms of anemia (fatigue, dyspnea, syncope). If the tumor is large, a moveable epigastric mass may be palpable.

**B Laboratory Findings.** The usual laboratory findings may be present.

**C X-ray Findings.** The x-ray is characterized by a smooth filling defect, clearly circumscribed, which does not interfere with normal peristalsis or peristalsis. Large tumors may have a small central crater visible on x-ray.

#### Treatment & Prognosis

If symptoms occur (particularly hemorrhage) surgical resection is necessary. The precancerous possibilities of adenomas have led many workers to favor their removal although many have been observed for years without malignant change.

Palmer E D. Benign intramural tumors of the stomach: a review with special reference to gross pathology. *Medicine* 30:81-181, 1951.

# DISEASES OF THE INTESTINES

## BACILLARY (SHIGELLA) DYSENTERY

### Essentials of Diagnosis

- Cramps and diarrhea, often with blood and mucus in the stools
- Fever, malaise, myalgia, prostration
- Pus in stools; organism isolated on stool culture
- Characteristic sigmoidoscopic findings

Bacillary dysentery must be distinguished from functional diarrhea, parasitic and viral infections, and diarrhea associated with chronic ulcerative colitis, and from salmonella or staphylococcal food poisoning

### General Considerations

Shigella dysentery is a common disease but it often occurs in mild or atypical forms and is unrecognized. Carriers often contribute to water- or milk-borne epidemics. Fly spread is important in areas of poor sanitation.

The infection may become localized and cause changes in the colon and the terminal ileum. Mucosal lymphoid hyperplasia, edema, and congestion progress to tiny follicular ulcers which enlarge and often become confluent. Mesenteric lymphadenitis is often present.

### Clinical Findings

**A. Symptoms and Signs** The onset is often abrupt, with diarrhea, lower abdominal cramps and tenesmus, anorexia, nausea, chills, malaise, myalgia, headache, and drowsiness. The disease may vary from almost asymptomatic, with a few soft stools daily, to quite severe, with frequent watery stools containing blood and mucus, severe general toxicity, and even convulsions. Prostration and dehydration are progressive. The abdomen is moderately tender but not rigid. Fever may be high, but is usually 38°-39° C. (102°-102° F) or less.

**B. Laboratory Findings** Polymorphonuclear leukocytosis, hemoconcentration, blood, mucus, and pus in the stools. Stool culture is positive for shigella strains (often difficult or impossible to isolate), and there is a transitory rise of agglutination titers, often with bizarre cross-reactions.

**C. On sigmoidoscopic examination** there is early punctate follicular hyperplasia on an

engorged mucosa progressing to punctate follicular bleeding ulcers and then large discrete or confluent ulcers.

### Complications

Complications include perforation and peritonitis (rare), anal excoriations and abscesses, and acute arthritis, manifested by painful effusion in a large joint.

### Treatment\*

**A. Emergency Measures (for Severe Cases)** Isolate the patient and use all contagious disease precautions. Combat dehydration and electrolyte imbalance by the liberal use of saline and dextrose solutions I.V. and, when necessary, potassium solutions. Urinary output should be kept at 1000-1500 ml/day. In the absence of specific severe intestinal infections which predispose to perforation, the cautious use of narcotics may be considered to reduce fluid loss and relieve pain. Watch for circulatory collapse and shock. Obtain a stool specimen for microscopic examination and culture.

**B. Specific Measures** The broad-spectrum antibiotics are now considered the drugs of choice, since many strains are now resistant to the sulfonamides. There is a significant variation in response of specific organisms in different individuals. Give one of the tetracyclines or, if essential, chloramphenicol (Chloromycetin®), 0.25-1 Gm. every 6 hours. Sulfadiazine is the sulfonamide of choice if antibiotics are not available. Give 2-4 Gm. stat with equal or double quantities of sodium bicarbonate, and follow with 1-2 Gm. every 4 hours. If diarrhea is severe, larger doses by mouth or parenteral sodium sulfadiazine may be necessary.

For very severe bacillary dysentery, serum treatment (in addition to antibiotics or sulfonamides) may be helpful. (1) Bacillary dysentery polyvalent antitoxin serum. Test for sensitivity and administer 30-100 ml. diluted tenfold in physiologic saline solution I.V. 3 times daily until the toxemia is overcome. (2) Shiga antitoxin serum. Administer as above in doses of 40-80 ml. in 500 ml. saline solution I.V. twice daily.

**C. General Measures** The patient should be isolated at bed rest and all body discharges, dirty bed linens, and bed clothing carefully disinfected. Rectal hygiene is important. When diarrhea is severe and patient is weak, it may be advisable to have the patient defecate

\*Chronic bacillary dysentery. Treat as for chronic nonspecific ulcerative colitis (see p 341).

on disposable absorbent pads or sheets to avoid exertion. Initial purgation therapy is probably not advisable. Local heat may be applied to the abdomen for pain. Phenobarbital 15-30 mg ( $\frac{1}{4}$ - $\frac{1}{2}$  gr) orally 3 or 4 times daily or pentobarbital sodium, 0 1-0 13 Gm ( $\frac{1}{2}$ -2 gr) orally p r n may be used if sedation is required. For severe pain give codeine phosphate 15 65 mg ( $\frac{1}{4}$  1 gr) orally or subcut p r n. Give camphorated tincture of opium (paregoric) 4-8 ml (1-2 dr) as necessary for pain and frequent loose bowel movement. Atropine sulfate 0 3-0 6 mg ( $\frac{1}{200}$ - $\frac{1}{100}$  gr) orally or subcut is effective for relief of cramps.

Adequate fluid intake by oral and parenteral routes should be forced to the limit of tolerance. Total oral fluid intake should be about 3 L/day during the acute phase. One liter or more of parenteral saline solution daily may be necessary to replace fluid and salt losses in profuse diarrhea.

Although starvation diets are undesirable, patients with severe bacillary dysentery should not be allowed to eat a normal diet for 6-8 weeks after the acute phase has subsided. Give parenteral feedings if necessary and evaluate bowel symptoms before adding the various dietary constituents. In the early acute stage give clear broths, rice water, albumin water, tea with lactose, barley water or apple juice (not cider) at frequent intervals. In the late acute stage, gradually add (as tolerated) boiled milk, cereals and strained fruit juices, toasted soda crackers or bread and gelatin desserts. In the subacute stage gradually add (as tolerated) mashed potatoes, boiled rice, boiled chicken, soft-cooked eggs, lean fish, scraped beef and custards and puddings.

### Prognosis

The uncomplicated disease lasts about one week. Antibiotics and general measures speed recovery and lower the mortality rate, which may be significant, particularly in infants and old people.

## FOOD POISONING

The term "food poisoning" usually refers to the acute intoxication which results from the noxious agents or enterotoxins produced by bacteria. This is in contrast to gastrointestinal disturbances which are actually the result of infection of the gastrointestinal tract with microbial organisms or which are due to vegetable, animal or chemical poisons. Food

poisoning is a result of poor hygiene in preparation, processing, storage, distribution, or handling of food. Food poisoning should be suspected in febrile gastrointestinal disturbances of acute onset, especially when more than one person in a family, group, or community is involved. Diagnosis is aided by a careful history and collection of specimens of suspected food, vomitus, and stools for laboratory study. Reporting to local health authorities is essential.

Treatment is symptomatic and supportive except in botulism, for which specific antitoxin is indicated. Perform gastric lavage and withhold food, sedation, and parenteral fluids. Liquid and soft diets are indicated in convalescence.

Organism	Onset After Ingestion	Severity
<i>Clostridium botulinum</i>	12-24 hours	Very severe often fatal
<i>Staphylococcus aureus</i>	1-6 hours	May be severe usually recover in 1-4 days
<i>Salmonella enteritidis</i>	8-24 hours	May be severe usually recover in 1-2 days
<i>Streptococcus faecalis</i>	5-20 hours	

Dack O M Current status of therapy in microbial food poisoning J A M A 173 929 32 1960

Meyer K F Food poisoning New England J Med 249 765 73 804-12, and 843 52 1953

## REGIONAL ENTERITIS

### Essentials of Diagnosis

- Intermittent bouts of fever, diarrhea and right lower quadrant pain in a young adult
- Fistula formation or right lower quadrant mass and tenderness
- X-ray evidence of abnormality of the terminal ileum

Acute regional enteritis may simulate acute appendicitis. Location in the terminal ileum requires differentiation from intestinal tuberculosis and lymphomas. The symptoms of regional enteritis also must be distinguished (by sigmoidoscopic examination) from those of ulcerative colitis.

### General Considerations.

Regional enteritis is a chronic inflammatory disease of the small intestine causing fever, weight loss, and disturbed bowel function. It generally occurs in young adults and runs an intermittent clinical course with mild to severe disability and frequent complications.

The etiology is not known. The terminal ileum is the typical primary site, but involvement may extend up to the duodenum and into the colon, at times as "skip lesions" with normal intestine intervening. There is marked thickening of the submucosa with lymphedema, lymphoid hyperplasia, and nonspecific granulomas, and often ulceration of the overlying mucosa. A marked lymphadenitis occurs in the mesenteric nodes.

### Clinical Findings.

**A. Symptoms and Signs** The disease is characterized by exacerbations and remissions. Abdominal pain, colicky or steady, in the right lower quadrant or periumbilical area, is present at some time during the course of the disease and varies from mild to severe. Diarrhea may occur, usually with intervening periods of normal bowel function or constipation. Fever may be low-grade or, rarely, spiking with chills. Anorexia, flatulence, malaise, and weight loss are present. Milk products and chemically or mechanically irritating foods may aggravate symptoms.

Abdominal tenderness, especially in the right lower quadrant, with signs of peritoneal irritation and an abdominal or pelvic mass in the same area, is usually present. The mass is tender and varies from a sausage-like thickened intestine to matted loops of intestine. The patient usually appears chronically ill.

**B. Laboratory Findings** There is usually a hypochromic (occasionally macrocytic) anemia and occult blood in the stool. The x-ray shows mucosal irregularity, ulceration, stiffening of the bowel wall, and luminal narrowing in the terminal ileum. Sigmoidoscopic examination may show an edematous hyperemic mucosa or a discrete ulcer when the colon is involved.

### Complications.

Isochorectal and perianal fistulas occur frequently. Fistulas may occur to the bladder or vagina and even to the skin in the area of a previous scar. Mechanical intestinal obstruction may occur. Nutritional deficiency due to malabsorption may produce a sprue-like syndrome. Generalized peritonitis is rare because perforation occurs slowly.

### Treatment & Prognosis.

**A. General Measures** The diet should be generous, high-calorie, high-vitamin, and adequate in proteins, excluding raw fruits and vegetables. Treat anemia, diarrhea, and avitaminosis as indicated. The poorly absorbed sulfonamides may exert a favorable effect. Salicylazosulfapyridazine (Azulfidine<sup>®</sup>) is the sulfonamide most often used. The initial dosage is 1-1.5 Gm. 4-8 times daily in equal doses, preferably with meals or taken with food. The drug is usually given in courses of 2 weeks on and one week off. With improvement, the dosage may be reduced to 0.5 Gm. t.i.d. Penicillin and the tetracyclines are best avoided because of their tendency to produce candidal or enterococcal diarrhea. Corticotropin and the cortisones may be beneficial in some patients with diffuse regional enteritis, some clinicians use cortisone and the adrenal steroids in ileitis when suppurative complications are not present. Experience indicates that long-term use of these agents may not be without hazard.

**B. Surgical Measures** Surgery may be necessary for the treatment of specific complications (e.g., abscesses, fistulas, intestinal obstruction, or hemorrhage). Short-circuiting operations may be necessary when involvement is extensive and complications are present.

Crohn, B. C., & H. Yarnis: Regional ileitis.

Grune & Stratton, 1958.

Zetzel, L.: Regional enteritis. New England J. Med. 254:690-5 and 1029-32, 1956.

### TUMORS OF THE SMALL INTESTINE

Benign and malignant tumors of the small intestine are rare. There may be no symptoms or signs, but bleeding or obstruction (or both) may occur. The obstruction consists either of an intussusception with the tumor in the lead or a partial or complete occlusion of the lumen by growth of the tumor. Bleeding may cause weakness, fatigability, light-headedness, syncope, pallor, sweating, tachycardia, and tarry stools. Obstruction causes nausea, vomiting, and abdominal pains. The abdomen is tender and distended, and bowel sounds are diminished or absent. Malignant lesions produce weight loss and extra-intestinal manifestations (e.g., pain due to stretching of the liver capsule, flushing due to carcinoid). In the case of a duodenal carcinoma, a peptic ulcer syndrome may be present. A palpable mass is rarely found.

If there is bleeding melena and hypochromic anemia occur X ray may show the tumor mass or abnormality in the small bowel if obstruction is present in the absence of obstruction it is extremely difficult to demonstrate the mass

### Benign Tumors

Benign tumors may be symptomatic or may be incidental findings at operation or autopsy Treatment consists of surgical removal

Benign adenomas constitute 25% of all benign bowel tumors Lipomas occur most frequently in the ileum the presenting symptom is usually obstruction due to intussusception Leiomyomas are usually associated with bleeding and may also cause intussusception Angiomas behave like other small bowel tumors but have a greater tendency to bleed

### Malignant Tumors

The treatment of malignant tumors and their complications is usually surgical

Adenocarcinoma is the most common malignancy of the small bowel occurring most frequently in the duodenum and jejunum Symptoms are due to obstructions or hemorrhage The prognosis is very poor Lymphomas are also first manifested by obstruction or bleeding Perforation or sprue may also occur Postoperative radiation therapy may occasionally be of value Sarcomas occur most commonly in the mid small bowel and may first be manifested by mass obstruction or bleeding The prognosis is guarded

Carcinoid tumors arise from the argentaffin cells of the gastrointestinal tract Ninety per cent of these tumors occur in the appendix and three fourths of the remainder occur in the small intestine (usually the distal ileum) The tumor secretes serotonin and the systemic manifestations consist of (1) paroxysmal flushing and other vasomotor symptoms (2) dyspnea and wheezing (3) recurrent episodes of abdominal pain and diarrhea and (4) symptoms and signs of right sided valvular disease of the heart The diagnosis is confirmed by finding 5 hydroxyindoleacetic acid in the urine The primary tumor is usually small and obstruction is unusual The metastases are usually voluminous and surprisingly benign Treatment is symptomatic and supportive surgical excision may be indicated if the condition is recognized before widespread metastases have occurred The prognosis for cure is poor but long term survival is not unusual

Darling R C & C E Welch Tumors of the small intestine New England J Med 260 397 408 1959

Mattingly T W & A Sjoerdsma The cardiovascular manifestations of functioning carcinoid tumors Mod Concepts Cardiovas Dis 25 337 41 1956

### MECKEL'S DIVERTICULITIS

Meckel's diverticulum a remnant of the omphalomesenteric duct is found in about 2% of persons more frequently in males It arises from the ileum 2 or 3 feet from the ileocecal valve and may or may not have an umbilical attachment Most are silent but various abdominal symptoms may occur The blind pouch may be involved by an inflammatory process similar to appendicitis its congenital bands or inflammatory adhesions may cause acute intestinal obstruction it may induce intussusception or in the 16% which contain heterotopic islands of gastric mucosa it may form a peptic ulcer

The symptoms and signs of the acute appendicitis like disease and the acute intestinal obstruction caused by Meckel's diverticulitis cannot be differentiated from other primary processes except by exploration Ulcer type distress if present is localized near the umbilicus or lower and more important is not relieved by alkalis or food If ulceration has occurred blood will be present in the stool Other laboratory findings often cannot be differentiated from those of appendicitis or other causes of obstruction Massive gastrointestinal bleeding and perforation may occur

Meckel's diverticulitis should be resected either for relief or for differentiation from acute appendicitis Surgery is curative

Michel M L Field R J & W W Ogden Jr Meckel's diverticulum an analysis of one hundred cases and the report of a giant diverticulum and of four cases occurring within the same immediate family Ann Surg 141 819 29 1955

### MESENTERIC VASCULAR OCCLUSION

#### Essentials of Diagnosis

- Severe abdominal pain with nausea fecal vomiting and bloody diarrhea
- Severe prostration and shock
- Abdominal distention tenderness rigidity
- Leukocytosis hemoconcentration



Differentiate from acute pancreatitis anoxic organic obstruction and a perforated viscus. The elevated amylase in pancreatitis, the characteristic x-ray picture of obstruction and free peritoneal air in perforation may differentiate these conditions.

### General Considerations

Mesenteric arterial or venous occlusion is a serious abdominal disorder. Venous thrombosis, often secondary to intra-abdominal disorders or surgery, is the more common of the two. Arterial occlusion is occasionally embolic but is more frequently thrombotic. Both occur more frequently in men and in the older age groups.

The superior mesenteric artery or its branches are often involved. The affected bowel becomes congested, hemorrhagic and edematous and may cease to function, producing intestinal obstruction. True ischemic necrosis then develops.

### Clinical Findings

**A Symptoms and Signs.** Generalized abdominal pain often comes on abruptly and is usually steady and severe, but it may begin gradually and may be intermittent with colicky exacerbations. Nausea and vomiting occur; the vomitus is rarely bloody but frequently contains feces. Bloody diarrhea and marked prostration, sweating and anxiety may occur. A history of abdominal surgery or inflammation or of an embolic source or arteriosclerosis may be elicited.

Shock may be evident. Abdominal distention occurs early, and audible peristalsis (evident early) may later disappear. Peritoneal irritation is demonstrated by diffuse tenderness, rigidity and rebound tenderness.

**B Laboratory Findings.** Hemoconcentration, leukocytosis (over 15,000 with a shift to the left) and often blood in the stool.

**C X-ray Findings.** A plain film of the abdomen shows moderate gaseous distention of the small and large intestines and evidence of peritoneal fluid.

### Treatment & Prognosis

**Treat shock** (see p. 2). **Surgical exploration** is indicated with minimal delay. Gangrenous bowel should be resected and an end-to-end anastomosis performed if feasible. When the infarction is due to embolization or isolated thrombus of the superior mesenteric artery, embolectomy or thrombectomy may be possible and should be attempted. Anticoagulants are not indicated.

The mortality rate is extremely high in the acute disease.

De Muth, W E, Jr, Fitts W T, Jr, & L T Patterson. Mesenteric vascular occlusion. *Surg Gynec & Obst* 108:209-23, 1959.

## INTUSSUSCEPTION

Intussusception is the prolapse of intestine into the lumen of the adjoining portion, causing intestinal obstruction. It is primarily a disease of infants and young children, predominantly males, but it can occur at any age. The most frequent site of intussusception is around the ileocecal valve, with ileum prolapsing into the cecum or colon. There is a marked tendency for the invaginated portion to progress with peristalsis of the investing bowel, and this may compromise the circulation of the invaginated portion and cause congestion, edema and gangrene. Any lesion of the intestine - Meckel's diverticulum, polyps, submucous tumors, ulcers - can provoke an intussusception, but in most cases in infants and children no such lesions are demonstrable.

### Clinical Findings

**A Symptoms and Signs.** The onset is with paroxysms of severe colicky abdominal pain and short periods of remission. Later the pain may be more steady. Vomiting often occurs early and may persist or may disappear. Diarrhea is usually present at the onset; blood and mucus are generally present in later stools. An abdominal mass is found in most cases when the examination is satisfactory (as under anesthesia) and varies from a small nodule to a sausage-shaped tumor, usually in the right abdomen and often more distinct during periods of pain. The mass may move during the progress of the intussusception. On rectal examination one may be able to palpate the mass or the head of the intussusception or, rarely, see its actual prolapse. There may be blood and mucus in the rectum. Dehydration and fever are late signs.

**B Laboratory Findings.** Blood and mucus in the stool may be present. With gangrene the WBC is elevated.

**C X-ray Findings.** Barium contrast x-rays may show the obstruction in the colon or cecum (rarely in the terminal ileum) and the head of the prolapsed portion may be out-

lined. Higher enteric intussusceptions show only the intestinal obstruction pattern on a plain film of the abdomen.

### Complications

Strangulation with gangrene, perforation, and peritonitis may occur in untreated intussusception.

### Treatment

Decompression of the bowel by intubation or enterostomy may be sufficient to relieve the intussusception. However, conservative decompression is usually not indicated in adults and should not be delayed for more than 24-36 hours. Barium enema reduction may be attempted in the early stages and is successful in a limited number of cases. (See Acute Organic Intestinal Obstruction below.) If there is no response to decompression or if signs of gangrene become apparent, surgical exploration and removal of the causative factor (e.g., polyp, Meckel's diverticulum, foreign bodies, carcinoma) is mandatory.

### Prognosis

Barium enema reduction in the early stage or operative reduction and resection, if necessary, give excellent results and recurrence is rare in the absence of a precipitating lesion. Spontaneous reduction of an intussusception can occur with repeated attacks.

Roper, A. Intussusception in adults. *Surg Gynec & Obst* 103:267-78, 1956.

## ACUTE ORGANIC INTESTINAL OBSTRUCTION

### Essentials of Diagnosis

- Colicky abdominal pain, fecal vomiting, constipation, borborygmus.
- Progressive shock, tender distended abdomen without peritoneal irritation.
- Audible high-pitched tinkling peristalsis or peristaltic rushes.
- X-ray evidence of gas or gas and fluid levels without movement of gas.
- Little or no leukocytosis.

Differentiate from other acute abdominal conditions such as inflammation and perforation of a viscus or renal or gallbladder colic. The absence of both rigidity and leukocytosis helps distinguish the obstruction from inflammation and perforation, the lo-

cation, radiation, and the absence of distention or fecal vomiting distinguish the colic. Differentiate also from mesenteric vascular disease and torsion of an organ (e.g., ovarian cyst). In the late stages of obstruction it may be impossible to distinguish acute organic intestinal obstruction from the late stages of peritonitis.

### General Considerations

Acute organic intestinal obstruction usually involves the small intestine, particularly the ileum. Major inciting causes are external hernia and band adhesions. Less common causes are gallstones, neoplasms, granulomatous processes, intussusception, volvulus, and internal hernia.

### Clinical Findings

**A Symptoms and Signs.** Colicky abdominal pain in the periumbilical area becomes more constant and diffuse as distention develops. Vomiting at first of a reflex nature associated with the waves of pain, later becomes fecal. Borborygmus and consciousness of intestinal movement, obstipation, weakness, perspiration, and anxiety are often present. The patient is restless, changing position frequently with pain, and is often in a shock-like state with sweating, tachycardia, and dehydration. Abdominal distention may be localized with an isolated loop, but usually is generalized. The higher the obstruction, the less the distention, the longer the time of obstruction, the greater the distention. Audible peristalsis, peristaltic rushes with pain paroxysms, high-pitched tinkles, and visible peristalsis may be present. Abdominal tenderness is absent to moderate and generalized, and there are no signs of peritoneal irritation. Fever is absent or low-grade. A tender hernia may be present.

**B Laboratory Findings.** With dehydration, hemoconcentration may occur. Leukocytosis is absent or mild. Vomiting may cause electrolyte disturbances.

**C X-ray Findings.** Abdominal x-ray reveals gas-filled loops of bowel, and the gas does not progress downward on serial x-rays. Fluid levels may be visible.

### Complications

Anoxic changes may occur initially due to volvulus, external or internal hernia, band obstruction of the closed loop type, and intussusception.

## Treatment.

**A. Conservative Measures** Fluid balance must be restored and maintained. The abdomen should be decompressed with a Levin tube or long intestinal tube and suction. If strangulation has not occurred conservative treatment (decompression alone) may be tried for 24-36 hours and is frequently successful in partial obstruction caused by adhesions. The patient must be constantly observed and surgical correction undertaken at the first indication of strangulation or if there is no improvement after 24-36 hours. In general, however, definitive treatment by intubation should not be attempted in complete large or small bowel obstruction.

With signs of improvement (cessation of pain, decreased distention, decrease in the volume of suction drainage, passage of gas and feces per rectum), constant suction can be replaced by intermittent suction (2 hours on, 2 off) and, after 24 hours, by gravity drainage while oral fluids are permitted by mouth. If oral fluid therapy is well tolerated and bowel function is maintained, the tube may be removed.

The failure to tolerate oral fluids is an indication to resume suction or surgical correction.

**B. Surgical Measures** Failure to respond to conservative therapy, the occurrence of strangulation, or the presence of a lesion frequently associated with strangulation (volvulus, hernia, obstruction, intussusception in adults, or complete obstruction by adhesions) is usually an indication for immediate surgical correction after fluid and electrolyte balance has been restored. Surgery consists of relieving the obstruction and removing the cause, and resecting any gangrenous bowel with end-to-end anastomosis.

## Prognosis.

Prognosis varies with the causative factor and is definitely improved by early relief of obstruction. This may be possible by intestinal intubation with decompression, but surgery is usually required.

Smith, G.A., Perry, J.F., Jr., & E.G. Yonehiro. Mechanical intestinal obstructions: a study of 1252 cases. *Surg Gynec. & Obst.* 100: 651-60, 1955.

## FUNCTIONAL OBSTRUCTION (Adynamic Ileus)

### Essentials of Diagnosis

- Continuous abdominal pain, distention, vomiting, and obstipation
- History of a precipitating factor (surgery, peritonitis, pain)
- Minimal abdominal tenderness, decreased to absent bowel sounds
- X-ray evidence of gas and fluid in bowel

The symptoms and signs of obstruction with absent bowel sounds and a history of a precipitating condition leave little doubt as to the diagnosis. It is important to make certain that the adynamic ileus is not secondary to an organic obstruction, especially anoxic, where conservative management is harmful and immediate surgery may be life-saving.

### General Considerations

Adynamic ileus is a neurogenic impairment of peristalsis which may lead to intestinal obstruction. It is a common disorder due to a variety of intra-abdominal causes, e.g., direct gastrointestinal tract irritation (surgery), peritoneal irritation (hemorrhage, ruptured viscus, pancreatitis, peritonitis), and anoxic organic obstruction. Renal colic, vertebral fractures, spinal cord injuries, pneumonia and other severe infections, uremia, and diabetic coma also may cause adynamic ileus.

### Clinical Findings

**A. Symptoms and Signs** There is mild to moderate abdominal pain, continuous rather than colicky, associated with vomiting (which may later become fecal) and obstipation. Borborygmus is absent. The symptoms of the initiating condition may also be present, e.g., fever and prostration due to a ruptured viscus.

Abdominal distention is generalized and may be massive, with nonlocalized minimal abdominal tenderness and no signs of peritoneal irritation unless due to the primary disease. Bowel sounds are decreased to absent. Dehydration may occur after prolonged vomiting. Other signs of the initiating disorder may be present.

**B. Laboratory Findings** With prolonged vomiting hemoconcentration and electrolyte imbalance may occur. Leukocytosis, anemia, and elevated serum amylase may be present depending upon the initiating condition.

**C X-ray Findings** X-ray of the abdomen shows distended gas-filled loops of bowel in the small and large intestines and even in the rectum. There may be evidence of air-fluid levels in the distended bowel.

#### Treatment.

Most cases of adynamic ileus are post-operative and respond to restriction of oral intake with gradual liberalization of the diet as the bowel function returns. Severe and prolonged ileus may require gastrointestinal suction and complete restriction of oral intake. Bowel distention tends to prolong the ileus. When conservative therapy fails it may be necessary to operate for the purpose of decompressing the bowel by enterostomy or cecostomy and to rule out mechanical obstruction.

Those cases of sdynamic ileus secondary to other disease (e.g., electrolyte imbalance, severe infection, intra-abdominal or back injury, pneumonitis) are managed as above plus treatment of the primary disease.

#### Prognosis

The prognosis varies with that of the initiating disorder. Adynamic ileus may resolve without specific therapy when the cause is removed. Intubation with decompression is usually successful in causing return of function.

Wangenstein, O. H. (editor). *Intestinal Obstructions*, 2nd ed. Thomas, 1955.

are usually easily differentiated by the characteristic x-ray patterns. Neutral stool fats, decreased pancreatic enzymes, and a normal to diabetic glucose tolerance curve differentiate the steatorrhea of pancreatic disease. Intestinal and mesenteric tuberculosis, although rare, may also mimic primary sprue.

#### General Considerations.

Sprue syndromes are diseases of disturbed small intestine function characterized by impaired absorption, particularly of fats, and motor abnormalities. Three basic entities comprise the group: the celiac disease of children, tropical sprue, and nontropical sprue. Celiac disease and nontropical sprue respond to gluten-free diets. The polypeptide gliadin is the offending substance in gluten. Tropical sprue does not respond to gluten-free diet. It is apparently a deficiency state which responds to folic acid.

Pathologic changes are minimal other than the marked wasting and the signs of multiple vitamin deficiencies. Mucosal atrophy in the small intestine is noted, and some observers have described degenerative changes in the myenteric nerve plexuses.

Rare secondary varieties of sprue syndrome in which the cause of the small intestine dysfunction is known include gastrocolic fistulas, obstruction of intestinal lacteals by lymphomas, Whipple's disease, extensive regional enteritis, and giardiasis.

however, is normal. Plasma carotene and proteins and serum calcium, phosphorus, cholesterol, and prothrombin are low. Gastric hypochlorhydria is present. The pancreatic enzymes are normal.

X-rays show a deficiency pattern in the small intestine: dilatation, segmentation, and irregular flocculation of barium, loss of the normal feathery mucosal pattern, and often excess gas in the dilated loops.

**B. Nontropical Sprue and Adult Celiac Disease.** These disorders are characterized by defective absorption of fat, protein, vitamin B<sub>12</sub>, carbohydrate, and water. Absorption of fat-soluble vitamins A, D, and K is impaired. Osteomalacia may ensue. Protein loss from the intestine may occur. Elimination of gluten from the diet may cause dramatic improvement.

**C. Celiac Disease and Infantile Gluten Enteropathy.** Onset is usually in early childhood, but symptoms persist into adult life. The anemia is usually hypochromic and microcytic. The complications of impaired absorption are more severe: infantilism, dwarfism, tetany, vitamin deficiency signs, and even rickets may be seen. Low plasma carotene is often used as a diagnostic criterion. Celiac disease responds to the elimination of wheat gluten from the diet.

#### Treatment.

The anemia of sprue is treated by means of oral iron administration when the anemia is hypochromic. The macrocytic anemia of nontropical sprue usually responds to cyanocobalamin (vitamin B<sub>12</sub>), 15-30 mcg I.M., 1-2 times per week, and then 10-15 mcg I.M. every 1-2 weeks after remission is obtained, or folic acid, 10-15 mg (1/6-1/4 gr) daily orally or I.M.

The diet should be high-calorie, high-protein, low-fat, and gluten-free. Prothrombin deficiency is treated by means of water-soluble vitamin K preparations orally or, if urgent, I.V. or I.M. For hypocalcemia or tetany give calcium chloride, phosphate, or gluconate, 2 Gm (30 gr.) orally t.i.d., and vitamin D, 5000-20,000 units. Vitamin supplements by mouth are also advisable in sprue.

The corticosteroids may be advantageous in certain sprue patients since they increase the absorption of nitrogen, fats, and other nutrients from the gastrointestinal tract.

#### Prognosis.

With proper treatment the clinical and hematologic response is good.

- Gardner, F.H.: Tropical sprue. *New England J. Med.* 258:791-6 and 835-42, 1958.  
 Paterson, J.C.: The sprue syndrome. *Am. J. M. Sc.* 231:92-108, 1956.  
 Ruffin, J.M., & others: "Wheat-free" diet in the treatment of sprue. *New England J. Med.* 250:281-2, 1954.

### INTESTINAL LIPODYSTROPHY (Whipple's Disease)

Whipple's disease is an uncommon malabsorption disorder of unknown etiology with widespread systemic manifestations. Histologic examination of the small bowel mucosa and mesenteric and peripheral lymph nodes reveals characteristic large, foamy mononuclear cells filled with cytoplasmic material which gives a positive periodic acid-Schiff (PAS) staining reaction. The disease occurs primarily in middle-aged men and is of insidious onset; the course, without treatment, is usually downhill. The clinical manifestations include abdominal pain, diarrhea, steatorrhea, gastrointestinal bleeding, fever, lymphadenopathy, polyarthritides, edema, and gray to brown skin pigmentation. Anemia and hypoproteinemia are common.

Treatment is symptomatic and supportive and the results are variable. Corticosteroids (or corticotropin) or tetracycline antibiotics are given over a protracted period. The prognosis is generally poor, although dramatic remissions occasionally occur following treatment.

- Gross, J.B., & others: Whipple's disease: report of four cases, including two in brother with observations on pathologic physiology, diagnosis, and treatment. *Gastroenterology* 36:65-93, 1959.  
 Holt, P.R., Isselbacher, K.J., & C.M. Jones: The reversibility of Whipple's disease: report of a case, with comments on the influence of corticosteroid therapy. *New England J. Med.* 264:1335-9, 1961.  
 Pute, R.H., & H. Tesluk: Whipple's disease. *Am J Med* 19:383-400, 1955.

### PSEUDOMEMBRANOUS ENTEROCOLITIS

Pseudomembranous enterocolitis is a necrotizing lesion of the gut which may extend from the stomach to the rectum. Grossly it

is characterized by a friable, grayish-yellow membrane loosely adherent to the underlying mucosa or submucosa. Microscopically, mucosal necrosis, leukocytes, and necrotic debris are enmeshed in the fibrin membrane. Gram-positive cocci and other bacteria may be present in the membrane. The etiology is not completely understood, but the evidence points to the enterotoxin of the hemolytic *Staphylococcus aureus* as the precipitating factor. Suppression of other intestinal bacteria by antibiotics leads to the overgrowth of staphylococci.

The disease usually becomes manifest from the second to twelfth day after surgery or after antibiotic therapy. The patient usually has had or is taking antibiotics. The initial symptoms are usually diarrhea and fever. Diarrhea is profuse and watery and the stools may resemble serum and have a peculiar necrotic odor. Some patients may show abdominal distention or vomiting. The patient's condition rapidly deteriorates, with tachycardia, hypotension, shock, dehydration, oliguria, and electrolyte and protein loss. Liquid stools may exceed 10 L/day. Leukocyte counts are normal or elevated. Hemocoagulation frequently occurs. Stools may contain membrane, leukocytes, and gram-positive cocci.

Pseudomembranous enterocolitis must be distinguished from other postoperative complications such as peritonitis, mesenteric thrombosis, and hypovolemia due to blood loss. The history of antibiotic therapy and major surgery are important in the differential diagnosis.

Antibiotics must be discontinued. If staphylococci are present, give vancomycin (Vanocin<sup>®</sup>), 250-500 mg I V every 6 hours, until toxicity subsides and staphylococci disappear from the stools. Combat dehydration and electrolyte depletion with electrolyte solutions containing sodium and potassium. Combat shock with blood, plasma, and corticosteroids, e.g., hydrocortisone (or equivalent), 50 mg I V every 6 hours until the BP is stable.

Pseudomembranous enterocolitis is an extremely grave condition. Mortality statistics vary from 60-90%.

Pearce, C., & P. Denicen. A study of pseudomembranous enterocolitis. *Am J Surg* 89:292-300, 1960.

Van Prohaska, J., & others. Pseudomembranous (staphylococcal) enterocolitis. *Internat Abstr Surg* 112:103-15, 1961.

## APPENDICITIS

### Essentials of Diagnosis

- Right lower quadrant abdominal pain and tenderness with signs of peritoneal irritation in children and young adults
- Anorexia, nausea, vomiting, constipation
- Low-grade fever and mild polymorphonuclear leukocytosis

Appendicitis must be differentiated from acute pelvic inflammatory disease, rupture or torsion of an ovarian cyst, acute renal colic or infection, acute mesenteric lymphadenitis, Meckel's diverticulum, and ruptured ectopic pregnancy. At times it may be difficult or impossible to differentiate some of the above from an acute appendicitis except by surgery. Right lower lobe pulmonary infections in children with pain referred to the right lower quadrant and diabetic acidosis must also at times be distinguished from acute appendicitis.

### General Considerations

Inflammation of the vermiform appendix is typically an acute disease of children and young adults. About 10% of people have an acute attack of appendicitis at some time.

The common initiating factor in appendicitis is obstruction of the blind pouch, usually by a fecalith. Retained secretions then cause increased pressure, circulation is impaired and bacteria invade the wall. In the early stages resolution may follow relief of the obstruction, but eventually the process is irreversible with diffuse inflammation of the wall, gangrene and perforation. Primary bacterial invasion either from the lumen or by hematogenous transfer, is probably rare.

### Clinical Findings

Clinical findings may be atypical in very young and very old people.

**A. Symptoms and Signs.** Characteristically there is abdominal pain, generally mild and often colicky and, at the onset, localized in the low epigastrium or periumbilical region. The pain gradually shifts to the right lower quadrant and becomes more steady and usually more severe. Suprapubic, right groin, or back pain may be present. Anorexia is almost always present. Nausea and vomiting are generally mild, occur early, and may subside with localization of the pain. Constipation is usually present, diarrhea is unusual.

Fever, when present, is usually low-grade. Abdominal tenderness in the right lower quadrant is often specifically localized over McBurney's point. Other areas of point tenderness vary with the position of the appendix. The tenderness becomes more widespread with progressive peritoneal irritation. Signs of peritoneal irritation are guarding, muscle rigidity, rebound tenderness, and referred tenderness.

Stretch of the psoas muscle may cause pain in retrocecal appendix when anterior signs are lacking, tenderness in the right rectal vault may be a confirmatory sign in retrocecal or pelvic appendicitis. Bowel sounds are decreased or absent.

**B Laboratory Findings** Slight leukocytosis usually progresses over the course of the illness. There is a high percentage of neutrophils and some immature forms. The urinalysis is usually normal except for occasional pyuria and ureteral involvement from a retrocecal appendix.

### Differential Diagnosis

Acute pelvic inflammatory disease is more commonly bilateral. Fever, toxicity and leukocytosis are more marked. Sedimentation rate is elevated. Pelvic or rectal tenderness and findings related to the reproductive organs are present.

Rupture or torsion of an ovarian cyst can sometimes be differentiated on pelvic examination, if not, surgery is needed.

In acute renal colic or infection the pain is localized higher in the flank and urinary findings are diagnostic.

Acute mesenteric lymphadenitis is difficult to differentiate except by exploration although localizing signs of peritoneal irritation are unusual.

Meckel's diverticulitis may be impossible to differentiate except surgically although localization is usually more toward the midline.

In ruptured ectopic pregnancy and ruptured ovarian cyst, the blood irritation caused by slow leakage may simulate appendicitis and surgery may be necessary for differentiation. Evidences of blood loss and shock differentiate the acute ruptured ectopic pregnancy.

Diabetic acidosis has a typical clinical picture. The abdominal pain is not localized.

Right lower lobe lung infections in children with referred pain to the right lower quadrant may be confused with appendicitis, but fever and toxicity are more marked, there are physical evidences of pulmonary disease, and the chest x-ray is positive.

In ruptured peptic ulcer there is a history of ulcer distress, a more acute onset, and the disease is more prostrating. A slow leakage down the gutter can simulate appendicitis.

### Complications

Gangrene causes increasing toxicity, fever, leukocytosis, a widening area of abdominal pain and tenderness, and often ileus.

Perforation and peritonitis cause further increase in toxicity, fever, leukocytosis, generalization of abdominal pain and tenderness, abdominal distention, and often recurrence of vomiting.

Appendiceal abscess may form with localization of the perforation by omental and other abdominal structures and gradual subsidence of acute symptoms, often leaving a palpable mass.

Adhesions may form either as a direct result of the inflammatory process or as a postsurgical complication.

Pyelophlebitis and liver abscess are rare. Subdiaphragmatic abscess is unusual but may occur late after acute infection.

### Treatment

**A Preoperative Care** Within 8-12 hours after onset the symptoms and signs of appendicitis are frequently indefinite. Under these circumstances a period of close observation is essential. The patient is placed at bed rest and given nothing by mouth. Laxatives are never prescribed. Parenteral fluid therapy is begun as indicated. Narcotic medications are avoided if possible but sedation with barbiturates or tranquilizing agents is not contraindicated. Abdominal and rectal examinations, WBC, and differential are repeated periodically. Abdominal films and an upright chest film are obtained if the diagnosis is not clear. In most cases of appendicitis the diagnosis is clarified by localization of signs to the right lower quadrant within 24 hours after onset of symptoms.

A gastric tube is usually inserted preoperatively. The stomach is aspirated and lavaged if necessary and the patient is sent to the operating room with the tube in place. If there is a marked systemic reaction with severe toxicity and high fever, preoperative administration of antibiotics (e.g., penicillin and streptomycin) is advisable.

**B Surgical Treatment** In uncomplicated appendicitis, appendectomy is performed as soon as fluid imbalance and other significant systemic disturbances are controlled. Little preparation is usually required. Early surgery has a mortality rate of a fraction of 1%. Mor-

bidity and mortality are due primarily to its complications—gangrene and perforation, when operation is delayed.

**C Antibiotic therapy** (e.g., penicillin with streptomycin or one of the tetracyclines, or with both streptomycin and a tetracycline) is advisable for 5–7 days or longer if abdominal fluid at operation was purulent or malodorous, if culture was positive or if the appendix was gangrenous.

**D Emergency Nonsurgical Treatment**  
When surgical facilities are not available, treat with antibiotics as above and supportive measures.

#### Prognosis

With accurate diagnosis and early surgical removal of the appendix, mortality and morbidity are minimal. Delay of diagnosis still produces significant mortality and morbidity if complications occur.

Recurrent mild attacks may occur if the appendix is not removed. "Chronic appendicitis" does not exist.

Campbell J A, & D C McPhail: Acute appendicitis. *Brit. M. J.* 1: 852–5, 1938.

### ACUTE MESENTERIC LYMPHADENITIS

#### Essentials of Diagnosis

- Constant right lower quadrant or periumbilical pain in a child
- Anorexia, nausea, vomiting, fever up to 39.4°C (103°F)
- Right lower quadrant tenderness with minimal or no peritoneal irritation
- Leukocytosis generally over 15,000
- History of recent or current upper respiratory infection

#### General Considerations

Mesenteric lymphadenitis is an acute benign inflammation of the mesenteric lymph nodes causing fever and abdominal pain. It is usually a disease of children, may be recurrent, and presents a major problem in differentiation from acute appendicitis, Meckel's diverticulitis, renal infection or colic, and right lower lobe pulmonary infections. In children with pain referred to the right lower quadrant, episodes are frequently preceded by or accompanied by upper respiratory infections, and bacterial or viral etiology has been suggested. True suppuration is rare.

#### Clinical Findings

**A Symptoms and Signs** There is an acute onset of abdominal pain in the right lower quadrant or periumbilical area, generally steady from the onset rather than colicky, and associated with nausea, vomiting, and anorexia. Diarrhea often occurs. Abdominal tenderness is mild to severe and usually greatest in the right lower quadrant. Point localization of pain is unusual. Peritoneal irritation and right vault tenderness are mild or absent. Fever to 37.8–39.4°C (100–103°F) is usually present.

**B Laboratory Findings** There is a polymorphonuclear leukocytosis with a shift to the left, generally over 15,000 and higher than would be expected from the findings.

#### Treatment & Prognosis

Exploration may be warranted to be certain that the patient does not have appendicitis. Complete resolution is the rule.

Donhauser, J L: Primary acute mesenteric lymphadenitis. *Arch. Surg.* 74: 528–30, 1957.

### INTESTINAL TUBERCULOSIS

In the United States, tuberculosis of the intestinal tract is almost always secondary to pulmonary tuberculosis. The incidence rises sharply in far-advanced lung disease.

The mode of infection is by ingestion of tubercle bacilli with the formation of ulcerating lesions in the intestine, particularly the ileocecal region, and involvement of the mesenteric lymph nodes.

Symptoms may be absent or minimal even with extensive disease. When present, they usually consist of fever, anorexia, nausea, flatulence, distention after eating, and food intolerance. There may be abdominal pain and mild to severe cramps, usually in the right lower quadrant and often after meals. Constipation may be present, but mild to severe diarrhea is more characteristic.

Abdominal examination is not characteristic, although there may be mild right lower quadrant tenderness. Fistula-in-ano may be evident. Weight loss occurs.

There are no characteristic laboratory findings. The presence of tubercle bacilli in the feces does not correlate with intestinal involvement.



X-ray examination reveals irritability and spasm, particularly in the cecal region, irregular hypermotility of the intestinal tract, ulcerated lesions and irregular filling defects, particularly in the right colon and ileocecal region; and pulmonary tuberculosis.

The prognosis varies with that of the pulmonary disease. The intestinal lesions usually respond to chemotherapy and rest when re-exposure to infecting material is prevented.

Gaines, W., Steinbach, H. L., & E. Lowenhaupt: Tuberculosis of the stomach. *Radiology* 58: 808-19, 1952.

## DISEASES OF THE COLON & RECTUM

### CHRONIC NONSPECIFIC ULCERATIVE COLITIS

#### Essentials of Diagnosis

- Bloody diarrhea with lower abdominal cramps.
- Mild abdominal tenderness, weight loss, fever
- Anemia, no stool pathogens
- Specific x-ray and sigmoidoscopic abnormalities

Differentiate from bacillary dysentery and amebic dysentery on the basis of specific stool pathogens. When rectal structures have developed, differentiate from lymphogranuloma venereum by history and Frei test. Other points in the differential are functional diarrhea, regional enteritis, intestinal neoplasm, and diverticulitis.

#### General Considerations.

Chronic ulcerative colitis is an inflammatory disease of the colon of unknown etiology characterized by bloody diarrhea, a tendency to remissions and exacerbations, and involvement mainly of the left colon. It is primarily a disease of adolescents and young adults but may have its onset in any age group.

The pathologic process is that of acute nonspecific inflammation in the colon, particularly the rectosigmoid area, with multiple, irregular superficial ulcerations. Repeated episodes lead to thickening of the wall with scar tissue and the proliferative changes in the

epithelium may lead to polypoid structures. The etiology is not known, and may be multiple.

#### Clinical Findings.

**A. Symptoms and Signs:** This disease may vary from mild cases with relatively minimal symptoms to acute and fulminating, with severe diarrhea and prostration. Diarrhea is characteristic, there may be up to 30 or 40 discharges daily, with blood and mucus in the stools, or blood and mucus may occur without feces. Constipation may occur instead of diarrhea.

Nocturnal diarrhea is usually present when daytime diarrhea is severe. Rectal tenesmus may be severe, and anal incontinence may be present. Cramping lower abdominal pain often occurs but is generally mild. Anorexia, dyspeptic symptoms, malaise, weakness, and fatigability may also be present. A history of food intolerance (milk products, spices) can often be obtained, and there is a tendency toward remissions and exacerbations.

Fever, weight loss, and evidence of toxemia vary with the severity of the disease. Abdominal tenderness is generally mild and occurs without signs of peritoneal irritation. Abdominal distention may be present in the fulminating form and is a poor prognostic sign. Rectal examination shows perianal irritation, fissures, hemorrhoids, fistulas, and abscesses.

**B. Laboratory Findings:** Hypochromic microcytic anemia due to blood loss is usually present. In acute disease a polymorphonuclear leukocytosis may also be present. The sedimentation rate is elevated. Stools contain blood, pus, and mucus but no pathogenic organisms. Hypoproteinemia may occur. In the fulminating disease electrolyte disturbances may be evident.

**C. X-ray Findings:** On x-ray the involvement may be regional to generalized and may vary from irritability and fuzzy margins in the mild case to pseudopolyps, decreased size of colon, shortening and narrowing of the lumen, and loss of haustral markings in the severe case. When the disease is limited to the rectosigmoid area, the barium enema may even be normal.

**D. Sigmoidoscopic changes:** are present in over 90% of cases and vary from mucosal hyperemia, petechiae, and minimal granularity in mild cases to ulceration and polypoid changes in severe cases.

### Complications

Pericollitis may develop with fever, increased pain and tenderness, and, at times even a palpable mass and x-ray evidence of narrowing. Frank perforation may occur.

Perianal disorders such as hemorrhoids, fissures, abscesses, strictures, prolapse, and rectovaginal or rectovesical fistulas can occur.

Malignant degeneration can take place, and the incidence of carcinoma is higher in people with chronic ulcerative colitis.

Deficiency disease can occur, presenting as retarded physical and sexual maturity (in disease starting in childhood), vitamin deficiency, fatty metamorphosis or cirrhosis of the liver, and osteoporosis.

Erythema nodosum, pyoderma gangrenosum, and acute arthritis may develop.

### Treatment

**A General Measures.** Bed rest is usually necessary only in the acute phase, but adequate rest periods can form an effective part of the daily routine of most patients. The diet should be bland, but as appetizing and nutritious as possible (high-calorie, high-protein, high-vitamin diet). For marked anorexia it is permissible at times to use other than bland foods if the patient so desires. These patients can often tolerate meat fairly well. If allergic factors are suspected, elimination diets may be employed to advantage. Supplementary vitamins may be administered, especially if nutrition is markedly disturbed.

The exact role of psychogenic factors has not been determined. In any case, anxiety-producing mechanisms should be evaluated when possible. These patients need considerable understanding and reassurance. Mild sedation is often necessary for nervousness. These patients often do well on the various antispasmodic-sedative mixtures.

The various antiperistaltic agents employed for any chronic diarrhea may be used. Narcotics should be avoided if possible except for severe acute diarrhea. Metamucil<sup>®</sup> or other vegetable mucilages may be used to increase stool bulk.

If there is a bleeding tendency (due to hypoprothrombinemia), treatment with menadione or other vitamin K preparations may be indicated.

Anti-infective agents are not specific or curative, but good results and longer remissions have been reported with their use. Many sulfonamide preparations have been used. In general, those which are poorly absorbed from the gastrointestinal tract are preferred. (1)

Salicylazosulfapyridazine (Azulfidine<sup>®</sup>), 2-8 G/day, (2) succinylsulfathiazole (Sulfasuxidine<sup>®</sup>) 3 Gm every 4 hours, or (3) phthalylsulfathiazole (Sulfathalidine<sup>®</sup>) 1.5 Gm every 4 hours (may be doubled in cases of severe diarrhea). Penicillin, streptomycin, or chloramphenicol may be indicated in certain instances of localized perforation or systemic infection.

Corticotropin and the cortisones induce remissions in some instances, and their use should be considered in severe cases and whenever clinical control is difficult and the activity of the disease is interfering with other treatment measures. They are usually given in courses of 1-3 months during exacerbations. They should be administered in high doses and gradually reduced as symptoms disappear. Activity recurs when the drugs are discontinued before the onset of the natural cyclical remission phase. At times the drugs are used most profitably as adjuvants in the control of acute exacerbations of the disease and should probably be avoided for long-term use.

**B Surgical Measures.** Surgery may be required if medical therapy is not successful after an adequate trial. Subtotal or total colectomy is the procedure of choice when surgery is indicated.

### Prognosis

The disease may have many remissions and exacerbations over many years. At times the course is fulminant. Permanent and complete cure on medical therapy is unusual and life expectancy is shortened. Medical measures control the majority of cases, but colectomy is necessary for severe disease and often in the presence of complications.

Crohn B B, & others. Ulcerative colitis as affected by pregnancy. New York State J Med 56:2651-7, 1956.

Watkinson G, Thompson H, & J C Golligher. Right-sided or segmental ulcerative colitis. Brit J Surg 47:337-51, 1960.

Zetzel L. Ulcerative colitis. New England J Med 251:610-5 and 653-8, 1954.

### CONGENITAL MEGACOLON (Hirschsprung's Disease)

Hirschsprung's disease is a congenital disorder characterized by massive dilatation of the proximal colon due to loss of propulsive function in the distal sigmoid and rectum. The basic pathophysiologic abnormality is absent or

reduced ganglion cells in the rectum and lower sigmoid with loss of propulsive activity in this segment. Dilatation and muscular hypertrophy above this level are compensatory.

Symptoms include recurrent fecal impactions that are relatively refractory to cathartics and more responsive to enemas, infrequent bowel movements, and an enlarging abdomen. The periods between defecations may be 3-4 weeks or longer. Stools are large and have an offensive odor. Secondary symptoms include displacement of the thoracic contents causing dyspnea, edema of the extremities, and audible borborygms.

Abdominal distention is often massive and associated with costal flaring. Fecal masses and gas-filled loops of bowel are palpable in the abdomen, and sluggish visible peristalsis may be evident. Signs of poor nutrition may be present, such as multiple vitamin deficiencies, emaciation, and retarded growth. Secondary signs such as abdominal hernia, thinning of the abdominal wall, and diastasis recti abdominis are frequently present.

X-ray shows a normal or narrowed segment in the lower sigmoid or rectum and a dilated proximal colon.

In mild forms treatment may consist only of dietary supervision (avoiding high residue foods) and giving stool-softeners and lubricating agents. Frequent enemas are necessary. Parasympathomimetic drugs are useful on occasion.

If surgery is necessary, the colon must be completely emptied and the gastrointestinal tract sterilized preoperatively. Cecostomy or colostomy is not definitive but is a useful preliminary step until definitive surgery is feasible or as a life-saving procedure in a critically ill child.

The surgical procedure of choice is abdominoperineal removal of the rectosigmoid, the so-called "pull-through" operation (Swenson).

Abdominoperineal resection and anastomosis will yield excellent results in 80% of cases.

Hlatt, R. B. A further description of the pathologic physiology of congenital mega colon and the results of surgical treatment. *Pediatrics* 21: 825-31, 1958.

Ward, R. C. Hirschsprung's disease. *Lancet* 1: 302-9, 1951.

## DIVERTICULOSIS & DIVERTICULITIS

### Essentials of Diagnosis

- Older person with left lower quadrant pain, constipation, and fever
- Left lower quadrant tenderness with or without a palpable tender mass
- Leukocytosis, blood may be present in the stool
- X-ray evidence of diverticula and area of narrowing

The constrictive lesion of the bowel shown on x-ray or sigmoidoscopic examination must often be differentiated from carcinoma of the colon. The x-ray appearance of a short lesion and abrupt transition to normal bowel, and the frequent occurrence of blood in the stool usually point to a carcinoma, but final differentiation can sometimes be made only by biopsy or at surgery.

### General Considerations

Diverticula in the colon become frequent with advancing age and in themselves cause no symptoms. The inflammatory complication, diverticulitis, probably affects 20-25% of diverticula at some time.

Diverticula may have all the coats of the large intestine (true diverticula) or may have only mucosa and serosa (false diverticula). Diverticulitis is most likely to occur in the latter type. Although diverticula may occur throughout the gut they are most common in the sigmoid colon.

Inflammatory changes in diverticulitis vary from mild infiltration in the wall of the sac to extensive inflammatory changes in the surrounding area (peridiverticulitis) with perforation or abscess formation. The changes are comparable to those seen in appendicitis.

### Clinical Findings

*Diverticulosis without diverticulitis is asymptomatic.*

**A. Symptoms and Signs.** There are commonly intermittent episodes of left lower quadrant cramping to steady and severe abdominal pain which may last for days. Relief is often obtained by passing flatus or a bowel movement. Constipation is usual but diarrhea may occur. Blood in the stool is found in about 20% of cases. Massive hemorrhage may occur. Dysuria and frequency may occur.

Left lower quadrant and left rectal vault tenderness may be mild or severe and signs

of peritoneal irritation may be present. In about half of cases there is a left lower quadrant mass. Low-grade fever is present with attacks.

**B Laboratory Findings** Polymorphonuclear leukocytosis occurs with acute attacks.

**C X-ray Findings** Barium enema may show the diverticula, spasm and hypermotility of the involved segment or irregular narrowing of a long segment of the lumen with fusiform ends and gradual transition to normal bowel.

**D Sigmoidoscopic examination** may demonstrate the diverticula and reveal fixation and narrowing at the rectosigmoid junction.

### Complications

Perforation, peritonitis and complete intestinal obstruction may occur but are rare. Abscess and fistula formation also occur. The fistula is usually vesico-sigmoid but may go to the skin or the perianal area.

### Treatment

Conservative management is preferred. Give a bland diet as tolerated and anticonstipation measures. Nonconstipating antacid coating powders and gels, vegetable oils (olive oil), mineral oil and vegetable gum laxatives may be used. Antibiotics should be given for acute diverticulitis. The preferred schedule is with penicillin, 600,000 units and streptomycin 0.5 Gm every 12 hours. Broad-spectrum antibiotics may be used.

Surgical resection may be indicated in the event of complications.

### Prognosis

The usual case is mild and responds well to dietary measures and antibiotics.

Boles R S, Jr, & S M Jordan. The clinical significance of diverticulosis. *Gastroenterology* 35:579-82, 1958.

Horner J L. Natural history of diverticulosis of the colon. *Am J Digest Dis (New Series)* 3:343-50, 1958.

## POLYPS OF THE COLON & RECTUM

Adenomatous polyps of the colon and rectum are common benign neoplasms which are usually asymptomatic but tend to undergo

malignant change. Their frequency is estimated at 5-10% in middle life, and the majority are within reach of the sigmoidoscope. Bleeding or occasionally alterations in bowel function may occur, but the majority are discovered incidentally.

Enquist I F. The incidence and significance of polyps of the colon and rectum. *Surgery* 42:681-9, 1957.

Rider, J A, & others. Polyps of the colon and rectum: their incidence and relationship to carcinoma. *Am J Med* 16:555-64, 1954.

## CANCER OF THE COLON

### Essentials of Diagnosis

- Dyspeptic symptoms and altered bowel function (constipation or diarrhea)
- Blood in the feces, unexplained anemia, weight loss
- Palpable mass involving colon
- Sigmoidoscopic or x-ray evidence of bowel lesion

Cancer of the colon may need to be differentiated from diverticulitis which is usually associated with fever and has a different x-ray appearance. Functional bowel distress may also simulate cancer of the colon.

### General Considerations

Carcinoma of the colon is a common neoplasm, particularly in men past 50. The left half of the colon is more frequently involved than the right.

### Clinical Findings

**A Symptoms and Signs** Profound weakness and pallor due to chronic blood loss or depressed erythropoiesis (or both) may occur in right colon lesions in the absence of digestive symptoms. However, bloody diarrhea or constipation, often episodic, is usually present. Obstructive symptoms, more common in left colon lesions, are generally chronic and incomplete and associated with cramping and borborygmus, although acute obstruction can occur. Gross blood in or on the stool and weight loss and cachexia are late findings. Findings include weight loss, a palpable mass in the colon and with metastasis, enlarged liver or rectal shelf.

**B. Laboratory Findings** The anemia is that of chronic blood loss, i.e., microcytic hypochromic. Occult blood is often found in the stool.

Barium enema shows an irregular filling defect or annular constriction which in low lying lesions may be visualized on sigmoidoscopic examination.

#### Complications.

Complications include metastases, obstruction, perforation (rare), and hemorrhage (rare).

#### Treatment.

The only curative treatment in cancer of the large bowel is wide surgical resection of the lesion and its regional lymphatics after adequate bowel preparation and appropriate supportive measures. When a significant degree of mechanical obstruction is present, a preliminary transverse colostomy or cecostomy is necessary. Even when the lesion is incurable, palliative resection may be of value to relieve obstruction, bleeding, or the symptoms of local invasion.

#### Management of the Bladder After Combined Abdominoperineal Resection.

Postoperative urinary retention occurs in one-fourth of abdominoperineal resections and persists longer than 3 months in 10% of cases. Formerly this was regarded as neurogenic, but present opinion holds that mechanical factors are largely responsible. Some degree of prostatism is frequently present, and is aggravated by loss of support of the base of the bladder, vesical neck, and prostatic urethra, so that the physiologic balance is disturbed and the bladder decompensates.

Constant bladder drainage with a Foley catheter is maintained for 7 days after a combined abdominoperineal resection. If by this time the patient is fully ambulatory and convalescence is normal, the catheter is removed in the morning and voiding is attempted. The amount of residual urine is determined that afternoon or evening. If more than 150 ml are present, either the catheter is replaced for 48 hours or the patient is catheterized several times at intervals of 8-10 hours. Even if voiding seems satisfactory, the patient should be catheterized for residual urine once daily for 2-3 days. If voiding is poor, bethanechol chloride (Urecholine®) may be helpful. In patients whose general condition and convalescence are satisfactory, ineffective conservative treatment should not be prolonged more than 3 weeks. Transurethral resection of the prostate is then done with immediate excellent results in about 90% of patients.

#### Care of the Colostomy.

The commonest permanent colostomy is the sigmoid colostomy made at the time of combined abdominoperineal resection. Abdominal distention must be avoided postoperatively by gastric tube suction until bowel activity returns. This is essential because tension on the colostomy involves the danger of retraction.

Colostomy irrigation is begun about one week after operation. Each day, a well-lubricated catheter or rectal tube is gently inserted about 15 cm (6 in.) into the colostomy and 500-1000 ml of water are instilled from an enema can or bag held 30-60 cm. (1-2 feet) above the colostomy. After the bowel has become accustomed to regular enemas, evacuation will occur within about one-half hour after the irrigation. Some individuals have regular movements without irrigation. A small gauze or disposable tissue pad worn over the colostomy, held in place by a wide elastic belt or ordinary girdle, is usually all the protection required during the day. For several months postoperatively the patient dilates the colostomy once daily by insertion of an index finger. Commercial colostomy kits make care simple and convenient.

Three important principles of colostomy management are a routine time for bowel evacuation, complete emptying after irrigation, and regulation of diet to avoid diarrhea. The patient with a colostomy can live a normal life.

Stricture, prolapse, and wound hernia are late colostomy complications requiring surgical correction. Skin irritation is less likely to occur than with ileostomy.

#### Prognosis.

Prognosis is good if resection is accomplished before nodal spread has occurred. The five-year cure rate is 50%.

Mutr, E.G.: The diagnosis of carcinoma of the colon and rectum: a review of 714 cases. *Brit J. Surg.* 44:1-7, 1956.

Weich, C.E., & W.P. Giddings: Carcinoma of colon and rectum: observations of Massachusetts General Hospital cases, 1937-1948. *New England J. Med.* 244:859-67, 1951.

## CANCER OF THE RECTUM

## Essentials of Diagnosis

- More frequent bowel movements with blood and mucus, tenesmus
- Palpation of tumor on rectal examination
- Visualization and biopsy on proctosigmoidoscopic examination

Cancer of the rectum must be distinguished from other causes of rectal bleeding such as hemorrhoids, fissures, and anal dermatitis. It is imperative in all cases of rectal bleeding to rule out carcinoma of the rectum or colon, which may occur concomitantly with benign lesions.

## General Considerations

Carcinoma of the rectum is the second most common malignancy in the gastrointestinal tract. It is predominantly a disease of man, usually over 50 years of age. Adenomas which have undergone malignant change are believed to be the initial lesions in many cases. These lesions tend to be polypoid or flat and ulcerated.

## Clinical Findings

**A. Symptoms and Signs.** Bowel movements are usually more frequent without changes in consistency of the feces. Tenesmus often occurs, and constipation and cramps may occur late. Vague dyspepsia and anorexia are late symptoms.

The tumor is usually palpable on rectal examination. Routine rectal examination may disclose an asymptomatic lesion.

**B. Laboratory Findings.** Blood and often mucus occur in the stool.

**C.** The tumor can be visualized and biopsied via proctosigmoidoscopic examination.

## Treatment.

Treatment is as for carcinoma of the colon.

## Prognosis

The five-year cure rate following surgical resection is about 50%.

Mayo, C. W., & O. A. Fly. Analysis of five year survival in carcinoma of the rectum and rectosigmoid. *Surg Gynec & Obst* 103:94-100, 1956.

## DISEASES OF THE ANUS

## HEMORRHOIDS

Internal hemorrhoids are varices of that portion of the venous hemorrhoidal plexus which lies submucosally just proximal to the dentate margin. External hemorrhoids arise from the same plexus but are located subcutaneously immediately distal to the dentate margin. Portal obstruction and pregnancy are important specific causes of hemorrhoids, but in most cases the etiology is obscure. Straining at stool, constipation, diarrhea, prolonged sitting, and anal infections are contributing factors and may precipitate complications such as thrombosis.

The symptoms and signs of hemorrhoids are painful defecation, rectal bleeding, and protrusion. The hemorrhoids can be seen with the anoscope. Rarely, hemorrhoids cause chronic bleeding which results in anemia.

In mild cases treatment consists of regulating bowel habits with stool softeners, e.g., dioctyl sodium sulfosuccinate (s.g., Colace®) or mineral oil and relieving pain with rectal suppositories e.g., Anusol®. Warm sitz baths may also provide relief.

Injection treatment may be indicated for mild cases or for severe cases if surgery is contraindicated or refused.

Hemorrhoidectomy is the treatment of choice in severe cases.

Hemorrhoids may divert attention from polyps, carcinoma, or other serious bowel disease. Therefore, rectal bleeding and anorectal symptoms must not be attributed to hemorrhoids until other conditions are ruled out. Before hemorrhoidectomy is performed, patients should be examined with the sigmoidoscope. A barium enema is indicated on all patients with a history of bleeding and routinely on all patients over 40.

## CRYPTITIS &amp; PAPILLITIS

Anal pain and burning of brief duration with defecation is suggestive of cryptitis and papillitis. Digital and anoscopic examination reveals hypertrophied papillae and indurated or inflamed crypts. Treatment consists of mineral oil by mouth, anorectal ointment (Nuzine®) or suppository (Anusol®) after each

bowel movement, and local application of 5% phenol in oil or carbol fuchsin compound to the crypts. If these measures fail, surgical excision of involved crypts and papilla should be considered.

### FISSURE-IN-ANO

Acute fissures represent recent breaks in the anal lining caused by the trauma of bowel movements. They usually clear if bowel movements are kept regular and soft (e.g., with mineral oil). The local application of a mild styptic such as 1-2% silver nitrate or 1% gentian violet solution may be of value.

Chronic fissure is characterized by (1) acute pain during and after defecation, (2) spotting of bright red blood at stool with occasional more abundant bleeding, (3) tendency to constipation through fear of pain, and (4) the late occurrence of a sentinel pile, a hypertrophied papilla, and spasm of the anal canal (usually very painful on digital examination). Regulation of bowel habits with mineral oil or other stool softeners, sitz baths and anal suppositories (e.g., Anusol<sup>®</sup>), b.i.d., should be tried. If these measures fail, the fissure, sentinel pile, or papilla and the adjacent crypt must be excised surgically. Postoperative care is along the lines of the preoperative treatment.

### ANAL ABSCESS

Perianal abscess should be considered the acute stage of an anal fistula until proved otherwise. The abscess should be adequately drained as soon as localized. Hot sitz baths may hasten the process of localization. The patient should be warned that after drainage of the abscess he may have a persistent fistula. It is painful and fruitless to search for the internal opening of a fistula in the presence of acute infection.

### FISTULA-IN-ANO

About 95% of all anal fistulas arise in an anal crypt and they are often preceded by an anal abscess. If an anal fistula enters the rectum above the pectinate line and there is no associated disease in the crypts, ulcerative colitis, rectal tuberculosis, lymphogranuloma

venereum, cancer, or foreign body should be considered in the differential diagnosis.

Acute fistula is associated with the chronic purulent discharge from the fistulous opening on the skin near the anus. There is usually local itching, tenderness, or pain aggravated by bowel movements. Recurrent anal abscesses may develop. The involved crypt can occasionally be located anoscopically with a cry hook. Probing the fistula should be gentle because false passages can be made with ease, and in any case demonstration of the internal opening by probing is not essential to the diagnosis.

Treatment is by surgical incision or excision of the fistula under general anesthesia. If a fistula passes deep to the entire anorectal ring so that all the muscles must be divided in order to extirpate the tract, a two-stage operation must be done to prevent incontinence.

### ANAL CONDYLOMAS

These wart-like papillomata of the perianal skin and anal canal flourish on moist, macerated surfaces, particularly in the presence of purulent discharge. They are not true tumors but are infectious and auto-inoculable, probably due to a virus. They must be distinguished from condylomata lata caused by syphilis. The diagnosis of the latter rests on the positive serologic test for syphilis or the discovery of *Treponema pallidum* on dark-field examination.

Treatment consists of careful application of 25% podophyllin in tincture of benzoin to the lesion (with bare wooden or cotton-tipped applicator sticks to avoid contact with uninvolved skin). Condylomas in the anal canal are treated through the anoscope and the painted site dusted with powder to localize the application and minimize discomfort. Electrofulguration under local anesthesia is useful if there are numerous lesions. Local cleanliness and the frequent use of a talc dusting powder are essential.

Condylomas tend to recur. The patient should be observed for several months and advised to report promptly if new lesions appear.

### BENIGN ANORECTAL STRICTURES

#### Congenital.

Anal contracture or stenosis in infancy may result from failure of disintegration of the

anal plate in fetal life. The narrowing is treated by careful repeated dilatation inserting progressively larger Hegar dilators until the anus admits first the little and then the index finger.

#### Traumatic

Acquired stenosis is usually the result of surgery or trauma which denudes the epithelium of the anal canal. Hemorrhoid operations in which too much skin is removed or which are followed by infection are the commonest cause. Constipation, ribbon stools and pain on defecation are the most frequent complaints. Stenosis predisposes to fissure, low-grade infection and occasionally fistula.

Prevention of stenosis after radical anal surgery is best accomplished by local cleanliness, hot sitz baths and gentle insertion of the well-lubricated finger twice weekly for 2-3 weeks beginning 2 weeks after surgery. When stenosis is chronic but mild, graduated anal dilators of increasing size may be inserted daily by the patient. For marked stenosis a plastic operation on the anal canal is advisable.

#### Inflammatory

**A. Lymphogranuloma Venereum.** This viral disease is the commonest cause of inflammatory stricture of the anorectal region. Acute proctitis due to lymphatic spread of the virus occurs early and may be followed by perirectal infections, sinuses and formation of scar tissue (resulting in stricture). Frei and complement fixation tests are positive.

The tetracycline drugs are curative in the initial phase of the disease. When extensive chronic secondary infection is present or when a stricture has formed, repeated biopsies are essential because epidermoid carcinoma develops in about 4% of strictures. Local operation on a stricture may be feasible but a colostomy or an abdominoperineal resection is often required.

**B. Granuloma Inguinale.** This disease may cause anorectal fistulas, infections and strictures. The Donovan body is best identified in tissue biopsy when there is rectal involvement. Epidermoid carcinoma develops in about 4% of cases with chronic anorectal granuloma.

The early lesions respond to tetracyclines. Destructive or constricting processes may require colostomy or resection.

## ANAL INCONTINENCE

Obstetric tears, anorectal operations (particularly fistulotomy), and neurologic disturbances are the most frequent causes of anal incontinence. When incontinence is due to surgery or trauma, surgical repair of the divided or torn sphincter is indicated. Repair of anterior laceration due to childbirth should be delayed for 6 months or more after parturition.

## SQUAMOUS CELL CARCINOMA OF THE ANUS

These tumors are relatively rare, comprising only 1-2% of all malignancies of the anus and large intestine. Bleeding, pain and local tumor are the commonest symptoms. Because the lesion is often confused with hemorrhoids or other common anal disorders, immediate biopsy of any suspicious mass or ulceration in the anal area is an essential diagnostic precaution. These tumors tend to become annular, invade the sphincter, and spread upward into the rectum.

Except for very small lesions (which can be adequately excised locally), treatment is by combined abdominoperineal resection. Radiation therapy is reserved for palliation and for patients who refuse or cannot withstand operation. Metastases to the inguinal nodes are treated by radical groin dissection when clinically evident. The five-year survival rate after resection is about 50%.

Hayden, E. P. Proctology. New England J Med 260:420-9, 1959.

Turell, R. Hemorrhoids: advances and retreats. Am J Surg 89:154-66, 1960.

## DISEASES OF THE LIVER & BILIARY TRACT

### JAUNDICE

#### Classification of Jaundice

A. Prehepatic. Hemolytic disorders

B. Hepatic

1. Congenital e.g., Dubin-Johnson syndrome



**Laboratory Examinations in  
Hepatocellular & Obstructive Jaundice**

Tests	Normal Values	Hepatocellular Jaundice	Uncomplicated Obstructive Jaundice
Bilirubin			
Direct	0.1-0.4 mg / 100 ml	Increased	Increased
Indirect	0.2-0.7 mg / 100 ml	Increased	Increased
Urine bilirubin	None	Increased	Increased
Urine urobilinogen	0.4 mg / 24 hours	Increased	Markedly decreased in complete obstruction
Stool urobilin	40-280 mg / 24 hours    Semi quantitative +1-20 -1-30	Unchanged or lowered	Decreased
Bromsulphalein retention (5 mg / Kg )	5% in 30 minutes    none in 45 minutes	Increased	Increased
Cephalin flocculation	0.1+	++ to ++++	0 to +
Thymol turbidity	0.4 units	Over 4 units	Not over 4 units
Serum protein	Albumin 3.4-6.5 Gm / 100 ml Globulin 2.3-5 Gm / 100 ml Total 5.7-8.2 Gm / 100 ml	Albumin decreased if damage severe A/G ratio reversed	Unchanged
Alkaline phosphatase	2.4-5 Bodansky units	Increased	Increased
Cholesterol			
Total	100-250 mg / 100 ml	Decreased if damage severe	Increased
Esters	60-75 mg / 100 ml	Decreased if damage severe	Normal
Prothrombin time	40-100% after vitamin K 15% increase in 24 hours	Prolonged if damage severe	Prolonged if obstruction marked
Serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) titers	SGPT 5-35 units SGOT 5-40 units	Increased in viral hepatitis	Usually unchanged may be increased

2 Hepatocellular e.g. hepatitis cirrhosis

3 Hepatocanalicular e.g. intrahepatic obstruction chlorpromazine toxicity

C Posthepatic Extrahepatic obstruction

1 Intermittent e.g. stone  
2 Complete e.g. carcinoma of pancreas

**Manifestations of Diseases Associated With Jaundice**

A Prehepatic Hemolysis weakness  
Abdominal or back pain may occur with acute

hemolytic crisis Normal stool and urine color Jaundice Splenomegaly is usually prominent except in sickle cell disease Hepatomegaly variable

B Hepatic Malaise anorexia low grade fever right upper quadrant discomfort Dark urine jaundice amenorrhea Enlarged tender liver vascular spiders palmar erythema ascites gynecomastia sparse body hair fetor hepaticus

C Posthepatic Colicky right upper quadrant pain weight loss (carcinoma) jaundice

dark urine, light stool Fluctuating jaundice and intermittently colored stools indicate intermittent obstruction from stone Blood in stools suggests malignancy Hepatomegaly, visible and palpable galbladder (Courvoisier's galbladder) Ascites, rectal shelf, and weight loss indicate malignancy Chills and fever suggest stone with cholangitis

1 anger, F M • The meaning of liver function tests Am J Med 16 565-73, 1954

Reinhold, J G Chemical evaluations of the functions of the liver Clin Chem 1 351 421, 1955

## VIRAL HEPATITIS

(Infectious Hepatitis & Homologous Serum Hepatitis)

### Essentials of Diagnosis

- Anorexia, nausea vomiting, malaise, symptoms of upper respiratory infection, aversion to smoking
- Fever enlarged, tender liver jaundice
- Normal to low WBC abnormal hepato-cellular liver function tests
- Liver biopsy characteristic

Differentiate viral hepatitis from other diseases that cause hepatitis or involve the liver such as Weil's disease, amebiasis cirrhosis infectious mononucleosis, and toxic hepatitis The prodromal phase or the nonicteric form of the disease must be distinguished from other infectious diseases such as influenza, upper respiratory infection and the prodromal stages of the exanthematous diseases In the obstructive phase of viral hepatitis it is necessary to rule out other obstructive lesions such as choledocholithiasis, chlorpromazine toxicity and carcinoma of the head of the pancreas Homologous serum hepatitis is clinically indistinguishable from infectious hepatitis

### General Considerations

Infectious hepatitis is a viral infection of the liver which may occur sporadically or in epidemics The liver involvement is a part of a generalized infection but dominates the clinical picture This disease is the most common infection of the liver, and often becomes a major health problem in crowded establishments, e g, military bases Transmission

of the virus is by the intestinal-oral route The virus is present in the feces and blood during the prodromal and acute phases, and often in asymptomatic carriers, and may persist for long periods without symptoms after the acute disease The incubation period is 2-6 weeks

Homologous serum hepatitis is a viral infection of the liver transmitted by the inoculation of contaminated blood or blood products The virus is similar to that which causes infectious hepatitis but is immunologically distinct, and little or no cross-immunity exists between the two diseases The virus is found only in the blood and tissues of an infected person and is never excreted via the intestinal tract The incubation period is 6 weeks to 6 months The pathologic findings are identical with those of infectious hepatitis Clinical features are also similar, but there is always a history of injection the disease is more common in the older age groups, and the onset is more often insidious than abrupt These facts with the longer incubation period, often allow clinical differentiation but in many cases the exact type cannot be determined

Pathologic findings in both diseases are varying degrees of necrosis of the parenchymal cells and cellular mononuclear exudation The reticulum framework is generally preserved, although it may become condensed Healing is by regeneration from surviving cells, usually without distortion of the normal architecture

### Clinical Findings

The clinical picture is extremely variable, ranging from asymptomatic infection without jaundice to a fulminating disease and death in a few days

#### A Symptoms

1 Prodromal phase - The speed of onset varies from abrupt to insidious with general malaise myalgia, fatigue, upper respiratory symptoms (coryza scratchy throat), and severe anorexia out of proportion to the degree of illness Nausea and vomiting are frequent, and diarrhea or constipation may occur Fever is generally present but is rarely over 39, 4°C. (103°F) Chills or chilliness may mark an acute onset

Abdominal pain is generally mild and constant in the upper right quadrant or right epigastrium, and is often aggravated by jarring or exertion A distaste for smoking may occur early in the illness

2 Icteric phase - Clinical jaundice occurs after 5-10 days but may be present at the onset, although many patients never develop clinical jaundice With the onset of jaundice there

is often an intensification of the prodromal symptoms followed by progressive clinical improvement

**3 Convalescent phase** - There is an increasing sense of well being, return of appetite, and disappearance of jaundice, abdominal pain, and fatigability

**B Signs** Hepatomegaly, rarely excessive and often variable from day to day, is present in over half of cases. Liver tenderness is often present. Splenomegaly is present in 15% of cases, and soft lymphadenopathy especially cervical, may occur. Signs of general toxemia vary from minimal to severe

**C Laboratory Findings** The WBC is normal to low, and abnormal lymphocytes (virus lymphocytes) may be present. Mild proteinuria is common, and bilirubinuria often precedes the appearance of jaundice. Acholic stools are often present during the initial icteric phase. Liver function tests tend to reflect hepatocellular damage with abnormal cephalin flocculation, BSP, thymol turbidity, and SGOT and SGPT values. There is decreased hippuric acid synthesis, and depression of cholesterol esters, increased gamma globulin, and urobilinogenuria. In the cholangiolitic variety the liver function tests may indicate obstruction as well.

Liver biopsy generally shows the characteristic pathology

#### Treatment.

**A General Measures** Bed rest is necessary until the initial acute symptoms have subsided and should be maintained judiciously until clinical and laboratory evidence of the acute disease has disappeared. Absolute bed rest beyond the most acute phase is not warranted. The return to activity during the convalescent period should be gradual. It is essential to keep a close check on the patient's actual intake and output during the acute phase. If (and only if) the patient is unable to take or retain food or fluids by mouth, give 10% glucose solution I.V. If the patient shows signs of impending hypoxic coma, protein should be restricted to 40 Gm./day and increased as improvement progresses. In general, dietary management consists of giving a palatable diet as tolerated. Patients with infectious hepatitis should avoid physical exertion, unnecessary transportation, alcohol, all medication whenever possible, especially barbiturates, morphine, and sulfonamides, and surgery, especially with general anesthesia.

Corticotropin or adrenal glucocorticoids are recommended only in the following circum-

stances: (1) If the patient's condition is deteriorating, (2) if serum bilirubin remains high ( $> 13 \text{ mg./100 ml.}$ ), or (3) if convalescence is prolonged (icterus index  $> 10 \text{ Gm./100 ml.}$  for 2 weeks or longer). These agents should not be given routinely in viral hepatitis.

#### Prevention

Isolation of infected individuals is recommended. Human immune globulin, 0.02-0.05 ml./lb., may prevent or ameliorate the disease if given to exposed persons during the incubation period. Avoid unnecessary transfusions, especially of possibly infected blood, serum, or plasma.

#### Prognosis

In the great majority of cases of infectious hepatitis clinical recovery is complete in 3-16 weeks. Laboratory evidences of disturbed liver function may persist longer. Over-all mortality is less than 1%, but is higher in older people (particularly in postmenopausal women). In a few cases the course is prolonged or asymptomatic are recurrent, with eventual full recovery. Cirrhosis of the portal or postnecrotic types or chronic progressive hepatitis develops infrequently.

Homologous serum hepatitis is a more severe illness than infectious hepatitis since it is more likely to occur in older persons, often as a complication of other diseases treated with blood or blood products. It occurs as a complication in 0.25-3% of blood transfusions and up to 12% of pooled plasma transfusions. The asymptomatic carrier state and persistent viremia after acute disease make control of contamination in donor blood extremely difficult.

- Krugman, S., & others. Infectious hepatitis. *J A M A* 174 823-30, 1950.  
Murray, R. Viral hepatitis. *Bull New York Acad Med* 31 341-58, 1955.  
Ward, R., & others. Infectious hepatitis: studies of its natural history and prevention. *New England J Med* 258 407-16, 1958.

#### VARIANTS OF INFECTIOUS HEPATITIS

##### Cholangiolitic Hepatitis.

There is usually a cholestatic phase in the initial icteric phase of infectious hepatitis, but in occasional cases this is the dominant manifestation of the disease. The course tends to be more prolonged than that of ordinary hepatitis, and biliary cirrhosis may de-

velop The symptoms are often extremely mild, but jaundice is deeper and pruritus is often present Laboratory tests of liver function indicate obstruction with marked hyperbilirubinemia elevated alkaline phosphatase and cholesterol, and normal flocculation reactions Differentiation from extrahepatic obstruction may be difficult even with liver biopsy

Gall, E A , & H Braunstein Hepatitis with manifestations simulating bile duct obstruction (So-called "cholangiolitic hepatitis ") *Am J Clin Path* 25 1113-27, 1955

Watson C J , & F W Hoffbauer The problem of prolonged hepatitis with particular reference to the cholangiolitic type and to the development of cholangiolitic cirrhosis of the liver *Ann Int Med* 25 195-227, 1946

### Fulminant Hepatitis

Hepatitis may take a rapidly progressive course terminating in less than 10 days Extensive necrosis of large areas of the liver gives the typical pathologic picture of acute liver atrophy Toxemia and gastrointestinal symptoms are more severe and hemorrhagic phenomena are common Neurologic symptoms of hepatic coma develop (see Portal Cirrhosis, below) Jaundice may be absent or minimal but laboratory tests show extreme hepatocellular damage

### Chronic Hepatitis

The persistence of symptoms 6 months or more after an acute episode of hepatitis presents a problem of differentiation of psycho-neurosis and hepatitis Anorexia, fatigability, vague dyspepsia and variable tenderness and enlargement of the liver are present Laboratory findings include hyperbilirubinemia positive flocculation tests bromsulphalein retention, urobilinogenuria, and increased gamma globulin Liver biopsy gives evidence of hepatitis The diagnosis of chronic hepatitis should be based on objective evidence of liver dysfunction and preferably liver biopsy in addition to symptoms

Chronic hepatitis may cause mild prolonged disability or it may progress to death

Kunkel, H G , Libby, D H , & C L Hoagland Chronic liver disease following infectious hepatitis 1 Abnormal convalescence from initial attack *Ann Int Med* 27 202-19 1947

MacDonald, R A , & G K Mallory The Natural history of postnecrotic cirrhosis a study of 221 autopsy cases *Am J Med* 24:334-57, 1958

## DRUG HEPATITIS

Hepatitis due to drug ingestion may assume two clinical courses, it may be indistinguishable from infectious hepatitis (hepatocellular type), or it may resemble obstructive jaundice (cholestatic type) The reaction may occur at any time during the administration of the drug It usually clears within a few weeks of discontinuance of the drug

Treatment consists of drug withdrawal and symptomatic and supportive measures as for acute hepatitis If the illness is severe, cortisone, 100 mg daily (or comparable doses of the various cortisone analogues), may be useful

Steigmann, F The early recognition of drug-induced liver disease *M Clin North America* 44 183-92, 1960

## FATTY LIVER

Fatty liver is due to chronic malnutrition It is primarily the result of excessive alcohol ingestion with poor dietary intake, but it is also seen in diabetic mellitus, obesity, kwashiorkor, and galactosemia The diagnosis depends upon the observation of hepatomegaly with relatively normal liver function and the characteristic fatty liver changes on biopsy

Levy, C M Fatty liver a study of 270 patients with biopsy proven fatty liver and a review of the literature *Medicine* 41: 249-76, 1962

## PORTAL CIRRHOSIS

### Essentials of Diagnosis

- Weakness, anorexia, gastrointestinal complaints right upper quadrant pain, hematemesis
- Hepatosplenomegaly, spider angiomas ascites dependent edema, mild jaundice, weight loss
- History of alcoholism or nutritional deficiency
- Hepatocellular dysfunction shown by liver function tests, esophageal varices
- Liver biopsy shows characteristic findings

Differentiation of portal cirrhosis from other types of cirrhosis may be difficult. Hemochromatosis occurs almost exclusively in males and is associated with pigmented skin. Post-necrotic cirrhosis occurs more often in women and in younger individuals, often with a history of infectious hepatitis. Biliary cirrhosis is marked by jaundice, hyperlipemia and skin pigmentation.

#### General Considerations

Portal cirrhosis is the most common form of chronic liver disease. It is due to many causes, but in a significant number of cases no cause can be determined. The following may play a role in etiology: malnutrition (especially vitamin B complex deficiency), alcoholism, hepatitis (rarely) chronic and repeated exposure to hepatotoxins, congenital syphilis, and infestations such as schistosomiasis, clonorchiasis and malaria.

The essential pathologic features are degeneration and necrosis of hepatic cells, often with fatty metamorphosis, nodular regeneration with loss of the normal lobular pattern and relationships to blood vessels and bile ducts, increased fibrous tissue usually in thin strands, bile duct proliferation, and inflammatory cell infiltration during phases of active parenchymal degeneration. The major distinguishing characteristic (from other types of cirrhosis) is the uniformity of the process; the nodules are less than 0.5 mm in diameter. Alteration of portal blood flow leads to congestive splenomegaly and other evidences of portal hypertension such as esophageal varices.

The incidence is higher in males and the age at onset is from 40 to 60 years.

#### Clinical Findings

**A. Symptoms and Signs.** Portal cirrhosis may cause no symptoms for long periods, both at the onset and later in the course (compensated phase). The onset of symptoms may be insidious or, less often, abrupt. Abrupt onset is usually precipitated by stress. Weakness, fatigability, and weight loss are common. Anorexia is always present and may be extreme, with nausea, flatulence, and often vomiting. Abdominal pain is due to gaseous or ascitic distention or more characteristically, consists of aching in the right upper quadrant or right epigastrium as a result of hepatic enlargement. Diarrhea is frequently present but some patients become constipated. Menstrual alteration (usually amenorrhea), impotence, loss of libido, sterility, and pain-

ful enlarged breasts in men (rare) may occur. Hematemesis is the presenting symptom in 15-25%.

In 70% of cases the liver is palpable, usually firm (due to fibrosis) and with a blunt edge. Skin manifestations consist of spider angiomas (generally only on the upper half of the body), palmar erythema (mottled redness of the thenar and hypothenar eminences), telangiectasis of exposed areas, and evidence of vitamin deficiency. Weight loss and the appearance of chronic illness are present. Jaundice, usually not a presenting sign, is generally mild except in the terminal phase. Ascites, hydrothorax, dependent edema and purpuric lesions are late findings; the precoma state (tremor, dysarthrias, rigidity, sluggish pupils, delirium, drowsiness) and coma are very late findings. Gynecomastia, pectoral and axillary alopecia and testicular atrophy may be present. Fever is present in 35% and splenomegaly in 35-50% of cases. The superficial veins of the abdomen and thorax are dilated (collateral circulation).

**B. Laboratory Findings.** In latent disease laboratory abnormalities may be absent or minimal. Anemia is a frequent finding. It is usually normocytic, rarely macrocytic. The WBC may be low, elevated or normal and may reflect hypersplenism. The sedimentation rate is increased. Coagulation abnormalities may be present as a result of failure of synthesis of clotting constituents in the liver. Proteinuria may be present and oliguria is frequent in active disease with ascites formation.

Liver function tests show primarily hepatocellular dysfunction. The BSP test is the most valuable means of identifying early cirrhosis.

Needle or surgical biopsy of the liver shows the characteristic pathology.

**C. X-ray Findings.** X-ray may reveal hepatosplenomegaly and esophageal or gastric varices.

**D. Esophagoscopy and gastroscopy** also demonstrate the varices when present.

#### Complications

Upper gastrointestinal tract bleeding may occur as a result of varices, hemorrhagic gastritis, or the not infrequently associated gastric and duodenal ulcers. Hemorrhage may be massive and fatal or may precipitate liver failure. Liver failure may also be precipitated by stress situations such as alcoholism, operations, and infections. Primary carcinoma of the liver and portal vein thrombosis occur.

more frequently in patients with cirrhosis. Lower resistance often leads to serious infections, especially pulmonary.

### Treatment.

**A. General Measures** The principles of treatment are abstinence from alcohol, rest during the acute phase, and adequate diet. The diet should be palatable, with adequate calories and protein (75-100 Gm /day) and, in the acute phase, sodium restriction. In the presence of ammonia intoxication, protein intake should be restricted also. Vitamin supplementation is indicated if deficiencies are present.

Corticotropin (ACTH) and the cortisones, if employed at all, should be used with careful consideration of the hazards hemorrhagic tendency, infection, and sodium retention. They should not be used in advanced cirrhosis of the alcoholic or dietary types.

### B. Special Problems

**1 Ascites and edema due to sodium retention, hypoproteinemia, and portal hypertension -**

(1) Low-sodium diet - Reduce sodium intake to 0.5-2 Gm NaCl daily or even less if necessary.

(2) Attempt to restore plasma proteins to normal levels. This is very difficult and should not be attempted at the risk of ammonia intoxication. Salt-poor albumin (very expensive) 50 Gm daily for about one week, may be employed in severe cases, but results are usually transient.

(3) Hydrochlorothiazide (Hydro-Diuril®), 25-50 mg 2-4 times daily or any of the other thiazide diuretics produces a marked increase in the excretion of sodium, potassium, and chloride. Observe carefully for hypokalemia.

(4) Spironolactone (Aldactone®), 100 mg q i d, acts as an aldosterone antagonist. It is most effective when used in combination with active diuretics such as hydrochlorothiazide, since potassium loss is reduced.

(5) Abdominal paracentesis for relief of pain, discomfort, or anorexia due to abdominal distention.

**2 Ammonia intoxication and "hepatic coma" -** Ammonia produced in bacterial decomposition of protein in the large bowel is either ineffectively removed by damaged liver cells or, because of portal obstruction, bypassed directly into the systemic circulation. The amount of ammonia produced is dependent upon the protein content, the bacterial flora, and the motility of the colon, and hepatic encephalopathy may be further aggravated by the invasion of colonic organisms through the

blood stream. Bleeding into the bowel from varices or ulcerations or as a result of bleeding tendencies may significantly increase the amount of protein in the bowel and precipitate rapid ammonia intoxication with encephalopathy and coma. Other factors which may precipitate hepatic coma include potassium deficiency, narcotics, hypnotics and sedatives, paracentesis, and hepatic or systemic infection.

(1) Dietary protein may be drastically curtailed or completely withheld for short periods if necessary, especially in acute episodes. Parenteral nutrition is usually indicated.

(2) Gastrointestinal bleeding should be treated by all necessary medical and surgical measures to remove blood and prevent further bleeding. Give milk of magnesia, 30 ml (1 oz) q i d or magnesium sulfate, 10-15 Gm by indwelling nasogastric tube.

(3) Control the intestinal flora with neomycin sulfate, 0.5-1 Gm every 6 hours for 5-7 days.

(4) Treat shock as outlined on p. 2.

(5) Treat infection with antibiotics chosen on the basis of culture and sensitivity studies. In some instances broad-spectrum antibiotics are indicated if the patient's condition is deteriorating.

(6) Arginine glutamate (Modumate®) 25 Gm as a 5% solution in 10% dextrose given I V and repeated in 8-12 hours if necessary, has sometimes proved useful in reduction of blood ammonia in (1) intoxication of exogenous origin, (2) portal cirrhosis with gastrointestinal hemorrhage, (3) patients with surgical shunts, and (4) acute hepatic insufficiency. Arginine has proved disappointing in chronic hepatic insufficiency.

(7) If agitation is marked give sodium phenobarbital, 0.13 Gm (2 gr) I M, or chloral hydrate 0.25-0.5 Gm (3 3/4-7 1/2 gr) by rectum cautiously as indicated. Avoid narcotics and CNS depressants.

**3 Anemia -** For hypochromic anemia, give ferrous sulfate, 0.2-0.3 Gm (3-4 1/2 gr) enteric-coated tablets, t i d after meals.

**4 Hemorrhagic tendency due to hypoproteinemia** may be treated with vitamin K preparations although this treatment is ineffective when intrahepatic damage is severe. Blood transfusions may be necessary to control the bleeding tendency. Give menadione, 1-3 mg orally t i d after meals, or menadione sodium bisulfite, 2 mg I V or I M every other day. If obstructive jaundice is present, give supplementary bile salts.

**5 Hemorrhage from esophageal varices -** Severe bleeding can at times be controlled by the use of the triple-lumen (Sengstaken) tube. In patients with a tendency to ammonia intoxication

cation who have hepatic encephalopathy or are in coma, this tube serves the combined purposes of hemostasis and removal of as much blood as possible. Surgical measures are usually hazardous and unsatisfactory, but surgery to relieve portal hypertension may be considered in selected patients. In younger patients in otherwise good condition in whom hepatocellular dysfunction is relatively slight portacaval anastomosis may be of benefit.

6 Pruritus, nausea and vomiting and constipation should be treated symptomatically.

7 Hemochromatosis - Intermittent bleeding over a period of many years (phlebotomy) of patients with "primary hemochromatosis" may have a beneficial and even remarkable effect.

#### Prognosis.

The prognosis in portal cirrhosis has been markedly improved during the past few years by dietary therapy. It is still grave in advanced cases, only 50% survive 2 years and only about 35% survive 5 years. Hematemesis, jaundice, and ascites are unfavorable prognostic signs. Many latent cases, however, do not shorten life and often are diagnosed only at autopsy.

Crews, R H , & W W Faloon. The fallacy of a low fat diet in liver disease. *J A M A* 181 754-60 1962

Davidson, C S. Cirrhosis of the liver. *Am J Med* 16 863-73, 1954

Jones, D P , & C S Davidson. The treatment of hepatic coma. *New England J Med* 267 195-8, 1962

Losowsky, M S , & C S Davidson. The treatment of cirrhosis of the liver. *New England J Med* 267 87-91 1962

Ratnoff, O D , & A J Patek, Jr. The natural history of Laennec's cirrhosis of the liver - an analysis of 386 cases. *Medicine* 21 207-68, 1942

#### POSTNECROTIC CIRRHOSIS

The clinical and laboratory findings in postnecrotic cirrhosis are indistinguishable from those of portal cirrhosis but the following are valuable clues to the diagnosis. Postnecrotic cirrhosis is not related to alcoholism, its incidence is higher in women and the age at onset is often below 40 in both sexes, the onset is frequently similar to that of acute viral hepatitis, jaundice is usually more intense and is present early in the course, ascites and peripheral edema are present

early, and hyperglobulinemia (predominantly gamma globulin) is consistently present and may reach extreme values (10 Gm /100 ml )

Treatment consists primarily of rest and palatable diet with adequate caloric content and, in acute cases, restriction of sodium. Adrenal steroids may be helpful if progressive hepatic decompensation occurs.

The present impression is that postnecrotic cirrhosis is more rapidly progressive and less responsive to dietary treatment than portal cirrhosis. The complications, however, are the same. Latent cases do occur and may not progress, but alter the onset of symptoms only 20% of patients survive 5 years.

Ratnoff, O S , & A J Patek. Postnecrotic cirrhosis of the liver. *J Chronic Dis* 1 266 91 1955

#### HEMOCHROMATOSIS

Idiopathic hemochromatosis is characterized by excessive iron absorption, with deposition of iron in the liver, pancreas, heart, adrenals, testes, and kidneys. Eventually the patient may develop hepatic, pancreatic, and cardiac insufficiency. The disease usually occurs in males and is rarely recognized before the second or third decade. Clinical manifestations include hepatomegaly and hepatic insufficiency, skin pigmentation (slate gray due to iron and brown due to melanin), cardiac enlargement and insufficiency, and diabetes mellitus with its complications. Bleeding from esophageal varices and hepatic carcinoma may occur.

Laboratory findings include elevated plasma iron, saturated iron-binding protein in plasma, and the characteristic liver biopsy stain for iron.

Treatment is directed at mobilization and removal of excess tissue iron by weekly phlebotomy of 500 ml of blood for many months (sometimes up to 2-3 years) until plasma iron and hematocrit determinations indicate depletion of iron stores. Symptomatic and supportive treatment of diabetic, hepatic, and cardiac complications may be necessary.

Although the long-term benefits of iron depletion therapy have not been completely established, available data indicate that the course of the disease may be favorably altered.

Finch, S C , & C A Finch. Idiopathic hemochromatosis, an iron storage disease. *Medicine* 34:381-430, 1955

Sheldon, J H.: Hemochromatosis. Oxford, 1935.

HYPERBILIRUBINEMIC STATES

Constitutional Hepatic Dysfunction (Gilbert's Disease).

This is a benign form of jaundice which must be distinguished from hemolytic disease and chronic hepatitis. The plasma bilirubin is primarily in the unconjugated form. The remainder of the laboratory examination is normal. Physical examination and liver biopsy are also normal. The prognosis is excellent.

Foulk, W.T., & others: Constitutional hepatic dysfunction (Gilbert's disease), its natural history and related syndromes. *Medicine* 38 25-46, 1959.

Familial Chronic Idiopathic Jaundice (Dubin-Sprinz-Johnson Syndrome).

This form of jaundice is believed to be due to a faulty excretory function of liver cells and is characterized by elevated serum bilirubin (conjugated form), elevated plasma bromo-sulphalein (conjugated form), normal alkaline phosphatase, and variable results on the flocculation tests. The gallbladder does not visualize on x-ray, and the liver biopsy shows a heavy pigmentation. Grossly the liver appears deep brown to black, microscopically it is heavily pigmented with a golden brown pigment.

The prognosis appears to be good. The defect is postulated to be in the excretory function of the liver cell.

Mandemo, E., & others: Familial chronic idiopathic jaundice (Dubin-Sprinz disease) with a note on bromsulphalein metabolism in this disease. *Am J Med* 28 42-50, 1960.

Rotor's Syndrome.

This is similar to Dubin-Sprinz-Johnson syndrome and, in fact, may be a variant of it. Pigmentation of the liver, however, does not occur in Rotor's syndrome.

Crigler-Najjar Syndrome.

This is a rare form of severe hereditary nonhemolytic jaundice, appearing shortly after birth, which is due to an absence of glucuronyl transferase. The baby accumulates unconjugated bilirubin and develops CNS disease resembling kernicterus.

There is no known treatment, and death usually occurs in infancy.

Crigler, J.F., Jr., & Najjar, V.A.: Congenital familial nonhemolytic jaundice with kernicterus. *Pediatrics* 10:169-80, 1952.

BILIARY CIRRHOSIS  
(Primary & Secondary)

Essentials of Diagnosis

- Jaundice, pruritus, right upper quadrant aching
- Hepatomegaly, xanthomas
- Abnormal liver function tests indicative of obstruction
- Good nutritional status with long-standing disease, history of extrahepatic obstructive lesion
- Liver biopsy often diagnostic

General Considerations.

Biliary cirrhosis is a chronic disease of the liver caused by interference with bile flow. The bile flow is most commonly obstructed in an extrahepatic site by calculi, neoplasm, scarring, or congenital atresia. Stasis alone may produce cirrhosis, but the frequently superimposed infection hastens the process. The less common intrahepatic obstructions may have no identifiable cause but have been noted to follow viral hepatitis, particularly the cholangiolitic type, and intrahepatic cholangitis. Some cases may be due to toxins. It is by far more common in women (particularly the intrahepatic type).

The pathologic findings vary with the cause and the stage of the process, but the following are characteristic: bile stasis with bile thrombi, pigmentation, extensive multiplication of bile ducts, nodular loss of normal architecture, marked cellular infiltration in the fibrous septa, little evidence of hepatic necrosis or regeneration, and absence of fatty metamorphosis. Bile lakes are characteristic of extrahepatic obstruction.

Clinical Findings.

A. Symptoms and Signs. In extrahepatic obstruction, symptoms of the primary lesion may predominate (e.g., carcinoma of the pancreas, choledocholithiasis). Jaundice and pruritus are initial symptoms. Jaundice is often marked and of varying intensity. Cholangitis may cause chills and fever. Mild right upper quadrant aching may be present. Anorexia, weight loss, and weakness may occur late in the illness.



The liver is enlarged and firm but usually not tender. Splenomegaly is a late finding when it occurs. The general signs of cirrhosis - ascites, peripheral edema, hematemesis, hemorrhagic manifestations in the skin and mucous membranes, bleeding gums, and epistaxis - are usually late manifestations. Spider angiomas and palmar erythema are not usually present. Xanthomatous lesions may occur in the skin of the eyelids, around the joints, and within tendons. Nutrition may remain good until the terminal phase.

**B. Laboratory Findings** The blood findings are normal except insofar as they reflect the inciting lesion. The stools are light-colored, frequent, and fatty, and stool urobilinogen is reduced. The urine is dark and contains bile. Liver function tests initially show a pattern of obstruction (elevated alkaline phosphatase and serum cholesterol, especially the free cholesterol fraction, decreased prothrombin, elevated bilirubin) but as obstruction persists - often complicated by infection - evidence of hepatocellular dysfunction appears (abnormal flocculation tests and reversed A/G ratio). Hyperlipemia, with a predominant increase in cholesterol and phospholipids, may reach extreme levels of over 3 Gm/100 ml. The serum, however, is not milky.

Liver biopsy, surgical or needle, usually demonstrates the typical pathologic findings although in late stages differentiation from other types of cirrhosis may be difficult.

**C. X-ray Findings** X-ray may show the inciting lesion or esophageal varices or, not infrequently, osteoporosis.

#### Treatment.

Exploration is indicated to establish the diagnosis of primary or secondary biliary cirrhosis. If no obstruction can be found with operative cholangiography, the only treatment is supportive: adequate nutrition, relief of itching, and, in some instances, adrenal steroids. Extrahepatic obstruction should be relieved if found. Treat any infection that is present with appropriate antibiotic drugs.

#### Prognosis

The intrahepatic form is generally progressive in spite of therapy, though spontaneous improvement may occur. Death due to liver failure, infections, or hemorrhage generally occurs in 5-10 years.

The course and prognosis of biliary cirrhosis secondary to extrahepatic obstruction depends upon the course of the inciting lesion.

If the obstruction can be relieved and any associated infection controlled, the cirrhosis in early stages will remain stationary.

- Ahrens, E H., Jr., & others. Primary biliary cirrhosis. *Medicine* 29: 299-364, 1950.  
 Sherlock, S. Primary biliary cirrhosis (chronic intrahepatic obstructive jaundice). *Gastroenterology* 37: 574-86, 1959.

## ACUTE CHOLECYSTITIS

### Essentials of Diagnosis

- Nausea, vomiting
- Severe right upper quadrant colicky pain and tenderness
- Fever and leukocytosis

The disorders most likely to be confused with acute cholecystitis are perforated peptic ulcer, acute pancreatitis, appendicitis in a high-lying appendix, perforated carcinoma or diverticulum of the hepatic flexure, liver abscess, liver congestion, acute viral hepatitis, and pneumonia with pleurisy on the right side. The diagnosis of uncomplicated acute cholecystitis is usually not difficult because of the definite localization of pain and tenderness in the right upper quadrant and the characteristic right infrascapular radiation.

### General Considerations

Cholecystitis is associated with gallstones in over 90% of cases. Acute cholecystitis is usually superimposed on a chronic process and is precipitated by obstruction of the cystic duct by a stone (or, rarely, by edema in the absence of calculi). There is rapid development of a tense, edematous, inflamed gallbladder. Infection often follows as a result of invasion by resident organisms.

### Clinical Findings

**A. Symptoms and Signs** A past history suggestive of chronic cholecystitis can often be obtained. The acute attack is frequently precipitated by a heavy meal and begins with right upper quadrant pain which usually radiates to the right infrascapular region. Pain is agonizingly severe and prostrating, and is associated with vomiting. Right upper quadrant tenderness is invariably present, and in most cases is associated with local muscle spasm and rebound tenderness. The tensely distended gallbladder is frequently palpable.

Minimal jaundice is occasionally present in the absence of common duct obstruction. Marked jaundice indicates choledocholithiasis or liver damage. Low-grade or moderate fever is present.

**B Laboratory Findings** Moderate leukocytosis is typical. Serum bilirubin levels of 1-4 mg/100 ml may be seen in the absence of common duct obstruction. Clinical jaundice appears when the bilirubin exceeds 2.5 mg/100 ml. Slight elevation of the serum amylase may rarely be noted.

**C X-ray Findings** Gallstones are found on plain abdominal x-rays in about 25% of cases of acute cholecystitis. I.V. cholecystography may be a useful emergency diagnostic procedure. If the gallbladder fills, acute cholecystitis is ruled out.

### Complications

**A Gangrene of the Gallbladder** Continued marked or progressive right upper quadrant pain, tenderness, muscle spasm, fever, and leukocytosis after 24-48 hours are suggestive of severe inflammation and possibly gangrene of the gallbladder. Necrosis may occasionally develop without definite signs, especially in the obese abdomen.

**B Cholangitis** Intermittent high fever and chills are the major signs. Common duct stone may be a contributing cause.

### Treatment

Acute cholecystitis will subside on a conservative regimen in the majority of cases. Cholecystectomy can then be scheduled 6 weeks to 3 months later when the patient's general condition is optimal and the technical difficulties of operation minimized. If, as occasionally happens, recurrent acute symptoms develop during this waiting period, cholecystectomy is indicated without further delay. When a program of conservative therapy is elected for acute cholecystitis, all patients (particularly the diabetic, the obese, and the elderly) must be watched carefully for signs of gangrene of the gallbladder.

Operation for acute cholecystitis is mandatory when there is evidence of gangrene or perforation. Operation during the acute stage is also justified as a means of reducing overall morbidity in good risk patients in whom the diagnosis is unequivocal. It is best to defer operation, if possible, in the presence of acute pancreatitis or common duct stone.

**A Conservative Treatment** During the acute period while the patient is being evaluated, the abdominal examination and WBC should be repeated several times daily. The principles of treatment are the same as in acute peritonitis (see p. 366) with the addition of an anticholinergic drug such as parenteral atropine or oral belladonna. Meperidine (Demerol<sup>®</sup>) is the analgesic of choice, since morphine produces spasm of the sphincter of Oddi. Antibiotics (e.g., penicillin and streptomycin or tetracycline alone, or the 3 drugs together in severe cases) are administered in all except mild, rapidly subsiding cases.

**B Surgical Treatment** When surgery is elected for acute cholecystitis, cholecystectomy is the operation of choice. The common duct should also be explored if indicated (see p. 361). In the poor risk patient or when technical difficulties with cholecystectomy arise, cholecystostomy is the safest procedure.

### Prognosis

Mild acute cholecystitis frequently subsides. However, the possibility of recurrence cannot be disregarded. Moderate or severe acute cholecystitis is an indication for surgery. Particularly in old people, it may result in serious complications which may be a threat to health and life. Surgery is most often curative.

Bartlett M K & W C Quinby Jr. Surgery of the biliary tract. I. Mortality and complications of cholecystectomy and choledochostomy for chronic cholecystitis. II. Treatment of acute cholecystitis (with G A Donaldson). New England J Med 254:154-6 and 200-5, 1956.

Byrne J J. Acute cholecystitis. Am J Surg 97:155-72, 1959.

## CHRONIC CHOLECYSTITIS

### Essentials of Diagnosis

- Recurrent colicky right upper quadrant pain
- Intolerance for fatty foods
- Epigastric distress, nausea

### Clinical Findings

**A Symptoms and Signs** When significant complaints occur, they fall into 2 general categories: (1) chronic dyspepsia with belching, flatulence, nausea, and other nondescript forms of indigestion, usually aggravated by

fatty foods and heavy meals, and (2) recurrent "biliary colic" characterized by attacks of right upper quadrant pain radiating to the right infrascapular region, lasting a few minutes or hours, occasionally accompanied by vomiting, and often precipitated by dietary indiscretion.

There are no specific physical findings except for transient, mild right upper quadrant tenderness during attacks of biliary colic. If hydrops of the gallbladder is present (rare) the tense, nontender organ can usually be palpated with ease.

**B Laboratory Findings** None are diagnostic. Serum bilirubin and liver function tests should be done, especially if common duct stone or liver disease is suspected.

**C X-ray Findings** Oral cholecystography is the most important diagnostic procedure. The presence of gallstones on plain films or cholecystography is presumptive evidence of cholecystitis. When there is simply nonfilling of the gallbladder, cholecystography is repeated with a double dose of the test medium. Alternatively, an I V cholecystogram can be ordered, particularly if common duct stone is suspected. If the gallbladder fails to visualize on the second examination it is probably diseased. Cholecystography is unreliable when there is significant liver dysfunction (BSP retention greater than 20%) common duct obstruction (serum bilirubin above 5%) malabsorption of the test material or in the presence of an acute abdomen due to any cause.

The noncalculous gallbladder which fills poorly and empties sluggishly is not a surgical problem, but because small stones may be easily overlooked in such cases cholecystography should be repeated if symptoms are especially suggestive of gallbladder disease. Sensitivity to iodine is the only contraindication to cholecystography.

### Differential Diagnosis

If there are attacks of typical biliary colic and x-ray evidence of cholelithiasis or a non-functioning gallbladder, the diagnosis is not difficult. When nonspecific dyspeptic symptoms are the chief complaint it is necessary to consider other gastrointestinal conditions. Among these are nervous dyspepsia, peptic ulcer, gastritis, chronic pancreatitis, and carcinoma of the stomach, pancreas, hepatic flexure, liver, or gallbladder. It is a good rule to obtain an upper gastrointestinal barium study on patients with suspected gallbladder disease because of the frequent coexistence of other disorders (especially peptic ulcer).

### Complications

The complications of chronic cholecystitis with cholelithiasis include acute cholecystitis, common duct stone, cholecystenteric fistula, pancreatitis, and carcinoma of the gallbladder.

### Treatment.

**A Medical Treatment** Conservative management is indicated for patients without clinical or x-ray evidence of stones who respond to careful medical treatment, for patients with a questionable diagnosis of gallbladder disease or low-grade symptoms (differentiation from functional dyspepsia is a difficult problem) for patients who refuse surgery, for poor risk patients, and for patients with a short life expectancy.

**1 Diet** - In general 2 types of diets are given a low-fat diet (classical type), which excludes both cooked and uncooked fats from all sources and a no-grease diet (modern concept) which excludes only the "cooked fats" (greases) which are nonemulsified at body temperatures but includes the uncooked fats such as are emulsified at body temperature. The first phase of the no-grease diet is similar to the Sippy I diet with frequent feedings of milk and cream as improvement occurs, the diet incorporates eggs, butter, cooked vegetables and fruit and cereals as tolerated.

**2 Antispasmodic medication** - Any of the following can be given: tincture of belladonna, 10 drops t i d before meals, belladonna extract 15 mg (1/4 gr) t i d before meals, phenobarbital-antispasmodic mixtures (see p 267) or atropine sulfate, 0.4-0.6 mg (1/150-1/100 gr) orally sublingually or subcut.

**3 Sedation** - Phenobarbital-antispasmodic mixtures (see p 323) and barbiturates.

**4 Dehydrocholic acid** (Decholin<sup>®</sup>), 0.25-0.5 Gm t i d after meals, may be used as a hydrocholoretic. Do not use this drug if biliary stasis is due to complete mechanical obstruction.

**B Surgical Treatment** Surgery is indicated in the following circumstances if the patient is a good surgical risk: (1) For good risk patients with biliary stones, with or without jaundice, who have recurrent attacks of right upper abdominal quadrant pain. Asymptomatic cholelithiasis in good risk patients is considered by some to be an indication for surgery. (2) For patients with suspicion of gallbladder malignancy. In general, cholecystectomy is preferred to palliative procedures except for poor risk or seriously ill patients or when there are technical contraindications. Cholecystostomy may also be indicated.

### Prognosis

The over-all mortality following cholecystectomy is less than 1%. However, biliary tract surgery is more complicated and hazardous in elderly patients, in patients over 70, cholecystectomy probably has a mortality of 5-10%.

After a properly performed operation, the patient usually is asymptomatic and requires no special diet or regimen.

Colcock, B P, & J E McManus. Experiences with 1356 cases of cholecystitis and cholelithiasis. *Surg Gynec & Obst* 101:161-72, 1955

## CHOLELITHIASIS

The high incidence of gallstones in the general population accounts for the clinical frequency of cholecystitis. Autopsy studies show that 32% of women and 16% of men past the age of 40 have gallstones. The incidence of calculi rises sharply at around 40 years of age. Pregnancy is an important predisposing cause of gallstones, and obesity may also be a contributing factor, hence the description of the typical gallbladder patient as "female, fat, and 40."

Gallstones usually consist of cholesterol, calcium bilirubinate, calcium carbonate, or a mixture of these. About 90% of the stones associated with chronic cholecystitis are of the mixed variety, whereas the preceding 3 types of "pure" calculi may be seen in a relatively normal gallbladder. Calcium bilirubinate stones tend to occur, sometimes at an early age, in such diseases as congenital hemolytic anemia and sickle cell anemia as a result of increased bilirubin in the bile.

Infection plays an important role in both cholelithiasis and cholecystitis. Chronic, low-grade bacterial involvement of the gallbladder produces cellular debris on which the various salts precipitate in the early stages of mixed stone formation. When mechanical obstruction of the cystic duct occurs, invasive infection of the distended gallbladder is common. Bacteria of intestinal origin (streptococci, coliform bacteria, and staphylococci) can be cultured from about half of calculous gallbladders removed at operation.

Gallstones are asymptomatic in two-thirds of cases, being discovered incidentally at operation or autopsy or on x-ray films. The management of asymptomatic gallstones is controversial, but most surgeons advise pro-

phylactic removal of the gallbladder if the patient is a reasonably good surgical risk. This opinion is based on the fact that at least one-third to one-half of these patients subsequently develop severe symptoms or complications such as acute cholecystitis or common duct stone. The chance of developing cancer of the gallbladder in the presence of cholelithiasis is probably slightly less than 1%.

Newman, H F, & J D Northrup. The autopsy incidence of gallstones. *Internat Abstr Surg* 109:1-13, 1959. In *Surg Gynec & Obst* 109, 1959.

## CHOLEDOCHOLITHIASIS (Biliary Colic)

### Essentials of Diagnosis

- Often a history of chronic indigestion, colic, or jaundice
- Sudden onset of severe RUQ or epigastric pain which may radiate to right scapula or shoulder
- Nausea and vomiting
- Fever, often followed by hypothermia or shock
- Jaundice, sometimes delayed
- Leukocytosis
- Plain films of abdomen may reveal gallstones

Cholelithiasis must be differentiated from right lower lobe pneumonia, perforated peptic ulcer, acute hepatitis, liver abscess, acute pancreatitis, right-sided renal colic, and acute intestinal obstruction.

### General Considerations

About 10% of patients with gallstones have cholelithiasis. The percentage rises with age, and the incidence in elderly people may be as high as 50%. Common duct stones usually originate in the gallbladder but may also form in the common duct. The stones are frequently "silent," as no symptoms result unless there is some obstruction.

### Clinical Findings

**A Symptoms and Signs.** A history suggestive of chronic cholecystitis can usually be obtained. The additional features which suggest the presence of a common duct stone are (1) frequently recurring attacks of biliary colic, (2) chills and fever associated with the attacks of colic, and (3) a history of jaundice.

Jaundice, which may be transient, is usually first noted within 1-2 days after an attack of colic. Occasionally there is no pain associated with the jaundice.

The presence of jaundice is strong evidence for common duct stone in a patient with a history of chronic gallbladder disease. Epigastric tenderness may occur during attacks of colic. Otherwise there are no specific abdominal signs.

**B Laboratory Findings** Liver function tests should be performed on all cases. Bilirubinuria and elevation of serum bilirubin are present if the common duct is obstructed. Elevation of the serum alkaline phosphatase is especially suggestive of obstructive jaundice. Because BSP retention is increased by duct obstruction, this test does not evaluate hepatocellular function under these circumstances. Prolongation of the prothrombin time begins to occur when bile is excluded for more than a few days from the gastrointestinal tract. When marked obstructive jaundice persists for several weeks, liver damage occurs and differentiation of obstructive from hepatocellular jaundice becomes progressively more difficult.

**C X-ray Findings** In the absence of significant jaundice, I V cholangiography will usually visualize the common duct. When jaundice is marked, plain abdominal x-rays are studied for biliary calculi.

#### Differential Diagnosis

The commonest cause of obstructive jaundice is common duct stone. Next in frequency is carcinoma of the pancreas, ampulla of Vater, or common duct. Metastatic carcinoma (usually from the gastrointestinal tract) and direct extension of gallbladder cancer are other important causes of obstructive jaundice. Hepatocellular jaundice can usually be differentiated by history, clinical findings, and liver function tests.

#### Complications

**A Biliary Cirrhosis** Prolonged common duct obstruction causes severe liver damage, hepatic failure or portal hypertension may be the ultimate result in untreated cases.

**B Cholangitis** The incidence of bacteria in common duct bile is 75% when calculi are present, the organisms most frequently cultured are *Escherichia coli*, *Aerobacter aerogenes*, *Streptococcus faecalis*, and *Proteus vulgaris*. Ascending infection is frequent in common duct stone, adds to liver damage, and may rarely lead to multiple liver abscesses.

**C Hypoprothrombinemia** Patients with obstructive jaundice or liver disease may bleed excessively at operation as a result of hypoprothrombinemia. If the prothrombin deficiency is due to faulty vitamin K absorption, the following preparations are of value (Parenteral administration is preferred to ensure complete absorption).

- 1 I V or subcut - Give one of the following
  - a Menadione sodium bisulfite (Hykinone<sup>®</sup>, Synkayvite<sup>®</sup>), 10 mg daily
  - b Phytonadione (Mephyton<sup>®</sup>), 10 mg daily
- 2 Orally - Give one of the following
  - a Menadione (Hykinone<sup>®</sup>, Synkayvite<sup>®</sup>), 5 mg b i d after meals. If there is obstructive jaundice, supplementary bile salts such as ox bile extract capsules or tablets must be given with menadione.
  - b Phytonadione (Mephyton<sup>®</sup>), 5 mg b i d

#### Treatment

Common duct stone is treated by cholecystectomy and choledochostomy.

**A Preoperative Care** Emergency operation is rarely necessary, a few days devoted to careful evaluation are well spent.

- 1 Liver function should be evaluated thoroughly.
- 2 Prothrombin time should be restored to normal by parenteral administration of vitamin K preparations (see above).
- 3 Glycogen and protein depletion should be combated by a high carbohydrate, high-protein, low-fat diet providing about 50 Calories and 2 Gm of protein/Kg body weight.
- 4 Vitamin supplements should be given.
- 5 Cholangitis, if present, should be controlled with antibiotics (e.g., a tetracycline, or penicillin and streptomycin).

**B Indications for Common Duct Exploration** At every operation for cholelithiasis the advisability of exploring the common duct must be considered. Operative cholangiography via the cystic duct is a very useful procedure for demonstrating common duct stone. Any of the following evidences of common duct stone may be an indication for choledochostomy.

- 1 Preoperative findings suggestive of choledocholithiasis include a history (or the presence) of obstructive jaundice, frequent attacks of biliary colic, cholangitis, history of pancreatitis, and an I V. cholangiogram showing stone, obstruction, or dilatation of the duct.
- 2 Operative findings suggestive of choledocholithiasis are palpable stones in the com-

mon duct dilated or thick walled common duct gallbladder stones small enough to pass through the cystic duct and pancreatitis

### C Postoperative Care

1 Antibiotics Postoperative antibiotics are not administered routinely after biliary tract surgery. Cultures of the bile are always taken at operation. If biliary tract infection was present preoperatively or is apparent at operation, penicillin and streptomycin or a tetracycline is administered postoperatively until sensitivity tests on culture specimens are available.

2 Management of the T tube Following choledochostomy a simple catheter or T tube is placed in the common duct for decompression. It must be attached securely to the skin or dressing because inadvertent removal of the tube may be disastrous. A properly placed tube should drain bile at the operating table and continuously thereafter; otherwise it is blocked or dislocated. The volume of bile drainage varies from 100-1000 ml daily (avg 200-400 ml). Above average drainages may be due to obstruction at the ampulla (usually edema), increased bile output, low resistance or siphonage effect in the drainage system, or a combination of these.

3 Cholangiography A cholangiogram through the T tube should be done on about the seventh or eighth postoperative day. Under fluoroscopic control a radiopaque medium (e.g. 50% Hypaque<sup>®</sup>) is aseptically and gently injected until the duct system is outlined and the medium begins to enter the duodenum. The injection of air bubbles must be avoided since on x-ray they resemble stones in the duct system. Spot films are taken. If the cholangiogram shows no stones in the common duct and the opaque medium flows freely into the duodenum, clamp the tube overnight and remove it by simple traction on the following day. A small amount of bile frequently leaks from the tube site for a few days. A rubber tissue drain is usually placed alongside the T tube at operation. This drain is partially withdrawn on the fifth day and shortened daily until it is removed completely on about the seventh day.

See reference under Cholelithiasis p. 360

## DISEASES OF THE PANCREAS

### ACUTE PANCREATITIS

#### Essentials of Diagnosis

- Abrupt onset acute epigastric pain often with back radiation
- Nausea vomiting prostration sweating
- Abdominal tenderness and distention fever
- Leukocytosis elevated serum amylase and lipase
- History of previous episodes or alcoholic or dietary excess

Acute pancreatitis may be almost impossible to differentiate from common duct stone or perforated peptic ulcer with elevated serum amylase. It must be differentiated also from acute mesenteric thrombosis, renal colic, dissecting aortic aneurysm, acute cholecystitis, and acute intestinal obstruction. The serum amylase may also be elevated in high intestinal obstruction, mumps, and after abdominal surgery or administration of narcotics.

#### General Considerations

Acute pancreatitis is the severe abdominal disease produced by acute inflammation in the pancreas and associated escape of pancreatic enzymes from the acinar cells into the surrounding tissue. The basic cause is not known and multiple factors may be responsible. Associated disease in the biliary system is common and reflux of bile into the pancreatic ducts via a common channel at the ampulla was the first mechanism proposed. The fact that acute pancreatitis can be precipitated by alcoholism or dietary excess suggests a secretory stimulus factor (perhaps with associated intraductal obstruction) is at work. Vascular and allergic causes have also been postulated. Surgical manipulation in the upper abdomen may also be followed by acute pancreatitis.

Pathologic changes vary from acute edema and cellular infiltration to necrosis of the acinar cells, hemorrhage from necrotic blood vessels, and intra- and extrapancreatic fat necrosis. A portion of the gland or the entire pancreas may be involved.

### Clinical Findings

**A Symptoms and Signs** Epigastric abdominal pain generally abrupt in onset is steady and severe and is often made worse by lying supine and better by sitting and leaning forward. The pain usually radiates into the back but may radiate to the right or left. Nausea, vomiting, and constipation are present and severe prostration, sweating, and anxiety are often present. There may be a history of alcoholic intake or a heavy meal immediately preceding the attack or a history of similar milder episodes in the past.

The abdomen is tender mainly in the upper abdomen, often with guarding or rigidity. The abdomen may be distended and bowel sounds may be absent in associated paralytic ileus. Fever of 38.3–38.9°C (101–102°F), tachycardia, hypotension (even true shock), pallor, and a cool clammy skin are often present. Mild jaundice occurs in 25% of cases. An upper abdominal mass may be present but is not characteristic.

**B Laboratory Findings** Leukocytosis (10,000–30,000), proteinuria, casts (25% of cases), glycosuria (10–20% of cases), hyperglycemia and abnormal glucose tolerance curves (50% of cases), and elevated serum bilirubin may be present. NPN and serum alkaline phosphatase may be elevated. Flocculation tests may be positive and coagulation tests abnormal. A decrease in serum calcium correlates well with the severity of the process. Depression is greatest on about the sixth day; levels below 7 mg/100 ml are associated with tetany and are an unfavorable sign.

The serum enzymes are elevated. Serum amylase is elevated early (in 90% of cases) and returns to normal by the third day; serum lipase rises more slowly and persists a few days longer. Plasma antithrombin titer (felt to be a measure of the blood trypsin level) is elevated early and may remain so after the amylase has returned to normal. Urine amylase and amylase activity in the peritoneal fluid (may be very high) remain elevated longer than serum amylase.

**C X-ray Findings** X-rays may show gallstones, a sentinel loop of gas distended small intestine in the left upper quadrant, or linear focal atelectasis or pleural fluid in the left pleural cavity. All of these findings are suggestive but not diagnostic of acute pancreatitis.

**D ECG Findings** ST-T wave changes may occur.

**E Peritoneal fluid** is yellow to reddish brown with microscopic fat globules and its pancreatic enzyme content is very high.

### Complications

Pancreatic abscess is a suppurative process in necrotic tissue with rising fever, leukocytosis, and localized tenderness and epigastric mass.

Pseudocyst (a cystic structure formed from necrotic areas) develops outside the pancreas and may become very large.

Chronic pancreatitis develops in 10% of cases.

Permanent diabetes mellitus and exocrine pancreatic insufficiency occur uncommonly.

### Prevention

All associated etiologic factors should be corrected, e.g., biliary tract disease, duodenal ulcers. The patient should be warned not to eat large meals or foods which are high in fat content.

The most common precipitating factor in acute pancreatitis is alcoholic indulgence.

### Treatment

**A Emergency Measures for Impending Shock** Place the patient at bed rest in the shock position and give morphine sulfate 15–20 mg (1/4–1/3 gr) subcut or I.V. or meperidine (Demerol®) 100–150 mg as necessary for pain. Atropine sulfate 0.4–0.6 mg (1/150–1/100 gr) subcut should be given as an antispasmodic.

Give 250–500 ml of plasma I.V. immediately and follow with subsequent infusions as necessary to correct disturbed fluid balance and maintain normal hematocrit. Five percent glucose or normal saline (or both) may be used initially if plasma is not available or to correct fluid and mineral imbalance.

Withhold food and fluids by mouth and initiate continuous gastric suction.

The patient should be constantly attended and vital signs should be checked every 15–30 minutes as indicated during the acute phase. Blood count, hematocrit, serum amylase, and serum lipase should be observed closely.

**B Follow-up** After the patient has recovered from shock (or if shock does not develop) it is necessary to choose between conservative or expectant medical management and exploratory surgery. Conservative therapy is preferred. Observe the patient closely for evidence of continued inflammation of the pancreas or related structures. A surgeon should be consulted in all cases of suspected acute pancreatitis. If the diagnosis is in doubt

and there is a possibility of a serious and surgically correctible lesion (e.g., perforated peptic ulcer), exploration is indicated.

When acute pancreatitis is unexpectedly found on exploration, it is usually wise to close without intervention of any kind. If the pancreatitis appears mild and cholelithiasis is present, cholecystostomy or cholecystectomy may be justified. In general, patients with unsuspected pancreatitis who receive the least intra-abdominal manipulation have the least morbidity and mortality after laparotomy.

The development of a pancreatic abscess is an indication for prompt drainage, usually through the flank. If a pseudocyst develops, it often requires surgical treatment.

The course of the inflammatory process should be observed by frequent physical examinations and blood counts and by blood sugar and serum and urine enzyme determinations as indicated. Antibiotic therapy should be reserved for patients with suppurative complications.

No fluid or foods should be given by mouth for at least 48 hours, and continuous gastric suction should be maintained for that period. After 48-72 hours, small quantities of bland, low-fat, liquid foods may be introduced gradually by mouth as tolerated. Gastric suction may be temporarily discontinued several times during the day for small oral feedings and then gradually discontinued, depending upon clinical progress. Give parenteral fluids as necessary to maintain fluid and electrolyte balance.

Atropine sulfate, 0.4-0.6 mg ( $\frac{1}{150}$ - $\frac{1}{100}$  gr) subcut., may be administered t.i.d. in an attempt to suppress pancreatic secretion.

**C. Convalescent Care** When clinical evidence of pancreatic inflammation has cleared, place the patient on a bland, low-fat diet and give belladonna extract, 15 mg ( $\frac{1}{4}$  gr) t.i.d., or atropine sulfate, 0.4-0.6 mg ( $\frac{1}{150}$ - $\frac{1}{100}$  gr) t.i.d. Antacids may be of value.

#### Prognosis.

Recurrences are common. The mortality rate is over 10% with medical supportive therapy. Surgery is indicated only when the diagnosis is in doubt or in the presence of associated disorder such as stones in the biliary tract. The mortality rate in these circumstances is higher than when surgery can be withheld.

Pollock, A.V.: Acute pancreatitis; analysis of 100 patients. *Brit. M. J.* 1:6-14, 1959.

Richman, A.: Acute pancreatitis. *Am J Med.* 21:246-74, 1956.

## CHRONIC RELAPSING PANCREATITIS

### Essentials of Diagnosis

- Repeated episodes of epigastric pain, often with back radiation, nausea, and vomiting.
- Fever, tachycardia, abdominal tenderness.
- Steatorrhea, impaired carbohydrate metabolism, elevated amylase.
- Pancreatic calcification.

Chronic relapsing pancreatitis must be differentiated from acute recurrent cholecystitis. With extensive fibrosis of the pancreas there may be common duct compression and differentiation must therefore be made from carcinoma of the pancreas and choledocholithiasis. Surgical exploration or biopsy may be required for definitive diagnosis.

### General Considerations

Chronic relapsing pancreatitis results from repeated episodes of pancreatic inflammation or degenerative changes in the organ itself, often producing pancreatic insufficiency. It is more common in males and may begin in early life. It may follow an attack of acute pancreatitis. Many cases are associated with alcoholism. Disease in the biliary tree is probably not important in the etiology.

The pathologic changes are those of focal necrosis and inflammation in the pancreas, leading to atrophy and fibrosis. Diffuse glandular calcification and duct stones occur. Fibrous replacement of pancreatic substance may progress rapidly or over long periods of time.

### Clinical Findings

**A. Symptoms and Signs** The course is episodic with relatively asymptomatic intervals. Symptoms include steady, mild to severe epigastric pain, lasting hours to days, with radiation frequently to the left hypochondrium, back, scapula, or left shoulder. Dyspepsia, nausea and vomiting, chills, fever, diarrhea or constipation, fat intolerance, and weight loss occur. The same symptoms in a less severe form may exist during periods of remission.

The patient appears chronically ill. Epigastric tenderness and occasional rigidity are present. Fever and tachycardia are common. Jaundice and a pancreatic mass are uncommon. The liver may be enlarged as a result of fatty degeneration.



**B Laboratory Findings** The stools are pale, bulky, and greasy, and float (steatorrhea) and contain undigested muscle fibers, neutral fats and soaps. During the acute attack leukocytosis, proteinuria, and glycosuria (in 33% of cases) may occur. True diabetes mellitus is present in up to 25% of cases; a decreased glucose tolerance is even more frequent. The serum amylase and lipase are usually elevated in an acute attack and reflect the severity of the attack, although in longstanding disease this elevation may not occur. The elevation may persist even during the intervals of remission. Bilirubinemia is frequently present during acute attacks.

**C X-ray Findings** X-ray examination may show evidence of biliary tract disease. Pancreatic calcification is present in half of patients, and may occur even without clinical evidence of pancreatitis. A widened or irregular duodenal loop, impaired motility of the stomach, or duodenal obstruction may be seen on gastrointestinal series.

#### Complications

Pancreatic insufficiency and pancreatic cyst or abscess may occur.

#### Treatment

There are no specific measures. Eliminate aggravating factors when possible, e.g. hepatobiliary or gastroduodenal disease, and forbid the use of alcohol. The diet should be high in carbohydrates and low in fat. Treat hypocalcemia with vitamin D and calcium administration, observe serum calcium carefully to prevent hypercalcemia. If diabetes mellitus is present, institute dietary and insulin therapy as required. Multivitamin tablets and B complex vitamins should be given. Treat pancreatic enzyme deficiency with pancreatin (Viokase®) 2 Gm orally t i d after meals. Detergent agents (e.g., sorbitan monooleate) are of doubtful value in correcting impaired fat and calcium absorption. Give ferrous sulfate, 0.2-0.3 Gm (3-4 1/2 gr) orally t i d after meals for hypochromic anemia.

#### Prognosis

Medical and surgical treatment are often unsuccessful in controlling recurrent episodes of pancreatitis. Pancreatic insufficiency may develop rapidly or may never appear. Treatment with insulin or pancreatic extract relieves many of the distressing symptoms.

Jones, R. F., & others. Chronic pancreatitis. Arch Int Med 105:320-3, 1960.

Lepore, M. J. The management of pancreatic insufficiency. M Clin North America 44:827-33, 1960.

## CARCINOMA OF THE PANCREAS

#### Essentials of Diagnosis

- Upper abdominal pain with back radiation, anorexia, marked weight loss, multiple venous thromboses.
- Occasionally a palpable abdominal mass, frequently, obstructive jaundice.
- Gastrointestinal series shows abnormality of duodenal loop or mucosa, impaired carbohydrate metabolism.

Pancreatic carcinoma involving the head of the pancreas must be differentiated from other causes of obstructive jaundice, particularly common duct stone and extrahepatic biliary tree neoplasm. Neoplasm involving the body and tail of the pancreas needs to be distinguished from other abdominal neoplasms involving the stomach, kidney and bowel. Chronic pancreatitis may give a similar clinical picture. The diagnosis is often very difficult, and may depend upon surgical exploration.

#### General Considerations

Carcinoma of the pancreas is a discouraging diagnostic and therapeutic problem. It is more common in males over 40 years of age. Most tumors are of duct cell origin; acinar cell tumors are rare. Lesions of the head of the pancreas are more common than those of the body or tail. Metastasis and direct extension (particularly to the perineural lymphatics) probably occur early.

#### Clinical Findings

**A Symptoms and Signs** The pain is constant in the epigastrium or left upper quadrant of the abdomen and is not related to meals or bowel function. It usually radiates into the back and is often aggravated by the supine position and relieved by bending forward. Anorexia is marked and weight loss occurs rapidly. Dyspepsia is a common complaint. Jaundice with pruritus occurs early in lesions of the head of the pancreas and late in those of the body and tail. Constipation or diarrhea and hematemesis may occur. Multiple venous thromboses occur early in 30-50% of patients with carcinoma of the body and tail.

The liver is enlarged and the gallbladder palpable in patients with jaundice. Epigastric or left upper quadrant tenderness is present. A mass is palpable in one-third of cases. Thrombophlebitis, particularly superficial, is common. Ascites is a late manifestation.

**B Laboratory Findings** There may be mild anemia. Glycosuria, hyperglycemia, and impaired glucose tolerance or true diabetes mellitus are found in 10-20% of cases. The serum amylase or lipase is occasionally elevated. Liver function responses are those of obstructive jaundice. Steatorrhea is rare. The secretin test of exocrine secretion is usually abnormal in volume, bicarbonate or amylase response. Duodenal cytology in a few cases has shown malignant cells.

**C X-ray Findings** X-ray examination is usually noncontributory in involvement of the body and tail. With carcinoma of the head of the pancreas the gastrointestinal series may show a widening of the duodenal loop, mucosal abnormalities in the duodenum ranging from edema to invasion or ulceration, or spasm or compression of the second portion of the duodenum.

### Treatment

Treatment is usually symptomatic and palliative, although radical surgical excision has been successful in selected cases. Biliary tract shunting procedures may be useful in cases associated with jaundice.

### Prognosis

The majority of cases are so far advanced at diagnosis that only palliative procedures are possible.

Clifton, E. E. Carcinoma of the pancreas.

Am J Med 21:760-80, 1956

Eyler, W. R., Clark, M. D., & R. L. Rian. An evaluation of roentgen signs of pancreatic enlargement. J A M A 181:967-72, 1962

## ACUTE PERITONITIS

### Essentials of Diagnosis

- Often a history of abdominal illness
- Relatively sudden onset of abdominal pain, vomiting, and fever
- Anxiety, confusion and prostration
- Abdominal rigidity and diffuse or local tenderness (often rebound)
- Later, abdominal distention and paralytic ileus
- Shock
- Leukocytosis

Peritonitis, which may present a highly variable clinical picture, must be differentiated from acute intestinal obstruction, acute cholecystitis with or without choledocholithiasis, renal colic, gastrointestinal hemorrhage, lower lobe pneumonias, porphyria, periodic fever, hysteria, and CNS disorders (e.g., tabes).

### General Considerations

Localized or generalized peritonitis is the most important complication of a wide variety of acute abdominal disorders. Peritonitis may be caused by infection or chemical irritation. Perforation or necrosis of the gastrointestinal tract is the usual source of infection. Chemical peritonitis occurs in acute pancreatitis and in the early stages of gastroduodenal perforation. Regardless of the etiology, certain typical features are usually present.

### Clinical Findings

**A Systemic Reaction** Malaise, prostration, nausea, vomiting, septic fever, leukocytosis, and electrolyte imbalance are usually seen in proportion to the severity of the process. If infection is not controlled, toxemia is progressive and toxic shock may develop terminally.

#### B Abdominal Signs

**1 Pain and tenderness** - Depending upon the extent of involvement, pain and tenderness may be localized or generalized. Abdominal pain on coughing, rebound tenderness referred to the area of peritonitis, and tenderness to light percussion over the inflamed peritoneum are characteristic. Pelvic peritonitis is associated with rectal and vaginal tenderness.

**2 Muscle rigidity** - The muscles overlying the area of inflammation usually become spastic. When peritonitis is generalized (e.g., after perforation of a peptic ulcer), marked rigidity of the entire abdominal wall may de-

velop immediately. Rigidity is frequently diminished or absent in the late stages of peritonitis. In severe toxemia, and when the abdominal wall is weak, flabby, or obese.

3 Paralytic ileus - Intestinal motility is markedly inhibited by peritoneal inflammation. Diminished to absent peristalsis and progressive abdominal distention are the cardinal signs. Vomiting occurs as a result of pooling of gastrointestinal secretions and gas. 70% of which is swallowed air.

C X-ray Findings Abdominal films show gas and fluid collections in both large and small bowel, usually with generalized rather than localized dilatation. The bowel walls when thrown into relief by the gas patterns may appear to be thickened, indicating the presence of edema or peritoneal fluid.

D Diagnostic Abdominal Tap Occasionaly useful.

#### Treatment

The measures employed in peritonitis as outlined below are generally applicable as supportive therapy in most acute abdominal disorders. The objectives are (1) to control infection, (2) to minimize the effects of paralytic ileus, and (3) to correct fluid, electrolyte and nutritional disorders.

A Specific Measures Operative procedures to close perforations to remove sources of infection such as gangrenous bowel or an inflamed appendix or to drain abscesses are frequently required. The cause of the peritonitis should always be identified and treated promptly.

B General Measures No matter what specific operative procedures are employed their ultimate success will often depend upon the care with which the following general measures are performed.

1 Bed rest in the medium Fowler (semi-sitting) position is preferred.

2 Nasogastric suction is started as soon as peritonitis is suspected. It is important to prevent gastrointestinal distention by the prompt institution of suction which is continued until peristaltic activity returns and deflation by rectum seems imminent or has begun. The gastric (e.g., Levin) tube is usually adequate in persistent paralytic ileus,

the intestinal tract may be more adequately decompressed by means of a long intestinal tube (e.g., Miller-Abbott), although passage of such a tube into the small bowel is frequently difficult because of poor intestinal motility. In rare cases combined gastric and long intestinal tube suction may be necessary to relieve or prevent distention.

3 Give nothing by mouth. Oral intake can be resumed slowly after nasogastric suction is discontinued.

4 Fluid and electrolyte therapy and parenteral feeding is required.

5 Narcotics and sedatives should be used liberally to ensure comfort and rest.

6 Antibiotic therapy. If infection with mixed intestinal flora is probably present, combined therapy with penicillin and streptomycin is begun empirically. It is often advisable to add a third antibiotic (e.g., tetracycline or chloramphenicol) to this regimen. When cultures are available, antibiotics are chosen according to sensitivity studies.

7 Blood transfusions are used as needed to control anemia.

8 Toxic shock if it develops requires intensive treatment.

#### Complications & Prognosis

The most frequent sequel of peritonitis is abscess formation in the pelvis, in the subphrenic space between the leaves of the mesentery or elsewhere in the abdomen. Antibiotic therapy may mask or delay the appearance of localizing signs of abscess. When fever, leukocytosis, toxemia or ileus fails to respond to the general measures for peritonitis, a collection of pus should be suspected. This will usually require surgical drainage. Abscess and pyelophlebitis are rare complications. Adhesions may cause early or, more frequently, late intestinal obstruction.

If the cause of peritonitis can be corrected, the infection, accompanying ileus and metabolic derangement can usually be managed successfully.

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Ann Surg 152:827-35, 1960.

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## 12...

# Diseases of the Breast

John L. Wilson

### DIFFERENTIAL DIAGNOSIS OF NIPPLE DISCHARGE

In order of frequency, the following lesions produce nipple discharge: intraductal papilloma, carcinoma, cystic disease, and ectasia of the ducts. The discharge is usually serous or bloody. When papilloma or cancer is the cause, a tumor can frequently be palpated beneath or close to the areola.

The site of the duct orifice from which the fluid exudes is a guide to the location of the involved duct. Gentle pressure on the breast is made with the fingertip at successive points around the circumference of the areola. A point will often be found at which pressure produces discharge. The dilated duct or a small tumor may be palpable here. The involved area should be excised by a meticulous technic which ensures removal of the affected duct and breast tissues immediately adjacent to it. If a tumor is present it should be biopsied and a frozen section done to determine whether cancer is present. When localization is not possible and no mass is palpable, the patient should be reexamined every week for one month. When unilateral discharge persists, even without definite localization or tumor, exploration must be considered. The alternative is follow-up at intervals of 1-3 months.

Cytologic examination of nipple discharge for exfoliated cells is indicated in all cases.

Ten to 20% of patients with serous or bloody nipple discharge prove to have carcinoma. Although none of the benign lesions causing nipple discharge are precancerous, they may coexist with cancer and it is not possible to distinguish them definitely from malignancy on clinical grounds. Patients with carcinoma almost always have a palpable mass, but in rare instances a nipple discharge may be the only sign. For these reasons chronic nipple discharge is usually an indication for exploration of the breast.

### MAMMOGRAPHY

A mammogram is a specialized soft tissue radiologic examination which shows promise as an adjunctive diagnostic procedure for suspected neoplasm of the breast. Special experience is required on the part of the radiologist in the technic and interpretation of this examination.

#### Indications.

Mammography is indicated for women with a strong familial history of breast carcinoma; nipple inversion or discharge without palpable findings; unexplained persistent breast pain; axillary masses; and secondary carcinoma of unestablished origin, and for women with recurrent lesions classed as suspiciously negative on biopsy.

#### Usefulness & Limitations.

The advantages of mammography are as follows: (1) It may demonstrate early and operable breast neoplasms when clinical findings are minimal or absent; (2) a negative result helps to confirm the surgeon's impression of the benign nature of a lesion; and (3) In proved carcinoma of the breast, mammography can at times demonstrate unsuspected carcinoma in the opposite breast.

However, false-negative findings may occur, the diagnosis is difficult when mammary tissue is very dense and compact (e.g., in adolescent girls), and special training and experience are required in taking and interpreting the films.

Egan, R. L.: Mammography, an aid to diagnosis of breast carcinoma. *J.A.M.A.* 182: 838-43, 1962.

Gerson-Cohen, J., Hermel, M. B., & S. M. Berger: Detection of breast cancer by periodic x-ray examination. *J.A.M.A.* 176: 1114-7, 1961.

## ADENOFIBROMA OF THE BREAST

This common benign neoplasm occurs most frequently in young women usually within 20 years after puberty. It is somewhat more frequent and tends to occur at an earlier age in Negro than in white women. Multiple tumors in one or both breasts are found in 10-15% of patients.

The typical adenofibroma is a round, firm, discrete, relatively movable, nontender mass 1-5 cm in diameter. The tumor is usually discovered accidentally. Clinical diagnosis in young patients is generally not difficult. In women over 30, cystic disease of the breasts, adenosis, and carcinoma must be considered. Treatment in all cases is excision and frozen section to determine if the lesion is cancerous.

Madalyn, H. E., Clagett, O. T., & J. R. McDonald. Lesions of the breast associated with discharge from the nipple. *Ann Surg* 146:751-83, 1957.

## CARCINOMA OF THE FEMALE BREAST

### Essentials of Diagnosis

- Single, nontender, firm to hard breast mass with ill-defined margins.
- Early findings: Minimal skin or nipple retraction.
- Later findings: Breast enlargement, hardness, redness, pain, fixation of mass to skin or chest wall.
- Late finding: Lymph node, bone, lung, or brain metastasis.
- Nipple erosion may be the only indication of early Paget's carcinoma.

Distinguish from cystic disease of the breast (frequently multiple, often recurrent, more discrete and tender breast masses), adenofibroma (occurs more frequently in younger females), intraductal papilloma (associated more frequently with nipple discharge), breast abscess (usually an inflammatory mass), and fat necrosis (there may or may not be a history of trauma).

### General Considerations

Carcinoma of the breast is the most common cause of death due to malignancy in women. The peak incidence is between the ages of 40 and 50, but breast cancer occurs frequently at all ages past 30. Differential diagnosis depends ultimately on biopsy.

Women with a family history of mammary carcinoma are at least twice as likely to develop the disease and tend to be affected at an earlier age. Because cystic disease of the breast is believed to be associated with an increased incidence of malignancy, continuous follow-up of patients with cystic disease is indicated.

Metastasis to regional lymph nodes is the principal mode of spread. Axillary metastases are found on microscopic study in 50-60% of patients undergoing radical mastectomy. The internal mammary nodes are invaded in about one third of patients who have clinically advanced disease of borderline operability. When the tumor is in the central or inner half of the breast and when the axillary nodes have already been invaded, the internal mammary chain is particularly likely to be involved.

Hematogenous spread of breast cancer is common to the bones (especially the pelvis, spine, femur, ribs, skull, and humeri), lungs, and liver are most frequently affected.

### Clinical Findings

**A. Symptoms and Signs.** The primary complaint in about 80% of patients with breast cancer is a firm lump (usually painless) in the breast. Less frequent symptoms are breast pain, erosion, retraction, enlargement, discharge, or itching of the nipple, and redness, generalized hardness, enlargement, or shrinkage of the breast. Rarely, an axillary mass, swelling of the arm, or back pain (from metastases) may be the first symptom.

Examination of the breast should be meticulous, methodical, and gentle. Careful inspection and palpation - with the patient supine, arms at her sides and overhead, and sitting, arms at her sides and overhead - are essential. Unless this procedure is followed at all physical examinations, early lesions will be missed. In some series, 5-10% of cases of breast carcinoma have been discovered during physical examinations performed for other purposes.

The frequency of carcinoma in various anatomic sites in the breast is as follows: Upper outer quadrant, 45%; lower outer quadrant, 10%; upper inner quadrant, 15%; lower inner quadrant, 5%; central (subareolar or diffuse), 25%.

Breast cancer usually consists of a nontender, firm or hard lump with poorly delimited margins (caused by local infiltration). Slight skin or nipple retraction is an important early sign. Minimal asymmetry of the breast may be noted. Very small (1-2 mm) erosions of the nipple epithelium may be the only manifestation of carcinoma of the Paget type. Watery

serous, or bloody discharge is an infrequent early sign. The following are characteristic of advanced carcinoma: edema, redness, nodularity, or ulceration of the skin, the presence of a large primary tumor, fixation to the chest wall, enlargement, shrinkage, or retraction of the breast, marked axillary lymphadenopathy, and distant metastases.

A lesion smaller than 1 cm in diameter may be difficult or impossible for the examiner to feel and yet may be discovered by the patient. She should always be asked to demonstrate the location of the mass, if the physician fails to confirm her suspicions, he should repeat the examination in one month. During the premenstrual phase of the cycle increased innocuous nodularity may suggest neoplasm or may obscure an underlying lesion. In these instances the patient should be asked to return after her period.

The axillary and cervical regions must be examined carefully for lymphadenopathy. The location, size, consistency and other physical features of all lesions should be recorded on a drawing of the breast for future reference.

#### B. Special Clinical Forms of Breast Carcinoma

1. **Paget's carcinoma**—The basic lesion is intraductal carcinoma, usually well-differentiated and multicentric in the nipple and breast ducts. The nipple epithelium is infiltrated, but gross nipple changes are often minimal and a tumor mass may not be palpable. The first symptom is often itching or burning of the nipple accompanied by a superficial erosion or ulceration. The diagnosis is readily established by biopsy of the eroded lesions.

Paget's carcinoma is not common (about 3% of all breast cancers) but it is important because it appears innocuous. It is frequently diagnosed and treated as dermatitis or bacterial infection. The lesion metastasizes to regional nodes in up to 60% of cases and should be treated in the same manner as other forms of breast cancer.

2. **Inflammatory carcinoma**—This is the most malignant form of breast cancer and comprises about 3% of all cases. The clinical findings consist of a rapidly growing, sometimes painful mass which enlarges the breast. The overlying skin becomes erythematous, edematous, and warm. The diagnosis should be made only when the redness involves more than one-third of the skin over the breast. The inflammatory changes, often mistaken for an infectious process, are caused by carcinomatous invasion of the subdermal lymphatics with resulting edema and hyperemia. Metastases occur early and widely in all cases, and

for this reason inflammatory carcinoma is virtually incurable. Radical mastectomy is not advised. Radiation and hormone therapy are of little value.

C. **Laboratory Findings**—A consistently elevated sedimentation rate or serum alkaline phosphatase is suggestive of widespread metastases.

D. **X-ray Findings**—Because of the frequency of metastases to the bones and lungs, preparation for a radical mastectomy should usually include posteroanterior and lateral chest films, anteroposterior and lateral views of the lumbar spine and pelvis, and a lateral skull x-ray.

#### Differential Diagnosis

Differential diagnosis depends upon biopsy. The following lesions are most likely to be confused with carcinoma: cystic disease of the breast, adenosis, adenofibroma (in the older patient), intraductal papilloma, and fat necrosis.

#### Treatment.

A. **Surgical Treatment**—All malignant lesions confined to the breast and axillary nodes should be treated by radical mastectomy if the patient's general health permits. Few patients, regardless of age, are unable to withstand a properly conducted operation.

The criteria of operability established by C. D. Haagensen in *Diseases of the Breast* (Saunders, 1956) are of great value in selecting patients who may benefit from surgical treatment. Haagensen advises radical mastectomy except when:

1. Extensive edema of the skin over the breast (more than one-third of the skin area) is present.

2. Satellite nodules are present in the skin over the breast.

3. The carcinoma is of the inflammatory type.

4. Any 2 or more of the following grave signs of locally advanced carcinoma are present: Ulceration of the skin, edema of the skin of limited extent (less than one-third of the skin over the breast), solid fixation of the tumor to the chest wall, axillary lymph nodes measuring 2.5 cm or more in transverse diameter, fixation of axillary nodes to the skin or deep structures of the axilla.

5. Edema of the arm is present.

6. Palpable supraclavicular nodes are present and biopsy shows metastases.

7. Biopsy of the internal mammary nodes in the first, second, or third interspaces or at the apex of the axilla reveals metastases. In-

ternal mammary biopsies are done for patients in whom (1) the primary tumor is situated in the lower parasternal zone of the breast, (2) the primary tumor measures more than 3 cm in diameter, (3) any of the 5 grave signs of locally advanced disease (see para 4 above) are present, (4) the axillary nodes are clinically involved. Apex of axilla biopsies are done for patients in whom (1) there is a single clinically involved axillary node measuring 2.5 cm or more in diameter, (2) there are more than 2 clinically involved nodes, (3) the node or nodes are fixed, (4) the primary tumor measures more than 5 cm in diameter, (5) any of the 5 grave signs of locally advanced disease (see para 4 above) are present.

8 Distant metastases are demonstrated by roentgenographic study of the chest by palpation of the liver, or by roentgenographic search for metastases in the skeletal system. In patients with pain in the back or pelvic area (suggesting vertebral metastases), trephine biopsy of the lumbar vertebrae may be considered if x-rays are negative.

The selection of candidates on the basis of Haagensen's criteria will limit radical mastectomy to patients for whom it may be curative. About 30% of patients chosen for internal mammary or apex of axilla biopsy on the basis of the indications outlined above will be found to have involved nodes in one or both of these locations. Such patients are not curable by surgery and should be spared radical mastectomy and treated by irradiation or with hormones. Multiple biopsies to determine operability should be done in a separate preliminary operation under general anesthesia.

B Radiotherapy The use of radiotherapy with or without simple mastectomy as the sole means of treating breast cancer is advisable only when the tumor is too advanced or the patient's condition too poor for radical mastectomy. Postoperative irradiation of the internal mammary, axillary, and supraclavicular regions may be of value when extensive axillary metastases are found on microscopic examination of the tissues removed by radical mastectomy. Local chest wall recurrence after radical mastectomy should be treated by x-ray rather than excision. Bone metastases, if sufficiently localized, are best managed by radiotherapy. Temporary relief of bone pain is obtained in 60-70% of such cases. Local palliation of large, ulcerated, or otherwise inoperable lesions is usually most successfully achieved by irradiation.

C. Hormone Therapy Hormone therapy is usually employed when surgery and irradiation have failed or when widespread metastases have rendered them useless. Hormone treatment does not cure but may retard the progression of the disease. The mode of action of hormones on breast cancer is not known. Therapy is of 2 types: (1) administration of one of the various estrogenic or androgenic hormones, or (2) removal of the ovaries, adrenals, or pituitary.

1 Estrogen therapy - Estrogens should be reserved for older patients, both because it is unwise to give estrogens to premenopausal women and because the effects are more beneficial in older women. In postmenopausal women estrogen produces regression of soft tissue carcinoma in about 50% of cases. Treatment usually consists of giving diethylstilbestrol, 5 mg t.i.d. (or equivalent) to a total dose of about 4 Gm. for maximal response, treatment should be continued as long as it is beneficial. The commonest side effects are anorexia, nausea, and vomiting, these usually disappear within a few weeks, but when symptoms of toxicity are severe the dosage should be reduced temporarily until tolerance is acquired. Pigmentation of nipples, areolas, and axillary skin, engorgement of the breasts and uterine bleeding may occur. Caution in patients with extensive bone metastases, estrogens may precipitate hypercalcemia followed by anuria and death.

2 Androgen therapy - Androgens give the best results in premenopausal women with soft tissue metastases or in patients with bone metastases at any age. Over half of patients report subjective improvement and regression of bone lesions is objectively observed in 20-30% of cases. Testosterone propionate is the most effective androgen preparation. The usual dose is 50-100 mg I.M. 3 times a week. About 3 months of treatment are required for maximal effect. Methyltestosterone is also effective and may be given in buccal tablets (50-100 mg daily) or orally (gradually increasing dosage from 0.3 Gm. daily to 1 Gm. daily). The favorable results of androgen therapy, aside from relief of pain, are a feeling of well-being and gain in weight. The principal side reactions are the masculinizing effects, e.g., hoarseness, hirsutism, loss of scalp hair, acne, and ruddy complexion.

3 Oophorectomy in premenopausal women with advanced, metastatic, or recurrent breast cancer results in temporary regression in about 25% of cases. Routine oophorectomy in all premenopausal women with breast cancer in the hope of lessening the incidence of recurrence after radical mastectomy has been



suggested but is not of proved value and cannot be recommended.

4. **Adrenalectomy or hypophysectomy** for advanced breast cancer is now under study. Regression occurs in about 30% of patients after either of these procedures, and life is usually prolonged in those patients who respond. Procedures to ablate the adrenals or pituitary may be considered in selected patients who fail to respond to hormonal therapy or oophorectomy.

D. **Chemotherapy** Chemotherapy should be considered for palliation in advanced breast cancer when hormone treatment is not successful or when the patient becomes unresponsive to it. Chemotherapy is most likely to be effective in patients who previously responded to hormonal therapy.

The most useful chemotherapeutic agent to date is 5-fluorouracil, but alkylating agents, particularly triethylenelophosphoramide (Thio-TEPA®) and nitrogen mustard, are also of value. These drugs are usually administered I.V. Their side effects include bone marrow depression and nausea and vomiting, which may be so severe as to limit or prevent their application. Intrapleural injection of nitrogen mustard will frequently control pleural effusion due to metastases if the fluid is exudative (specific gravity above 1.016 and a relatively high protein content).

#### Complications of Radical Mastectomy.

Except for local recurrence, usually due to implantation of tumor cells in the wound at operation, the only important late complication of radical mastectomy is edema of the arm. Significant edema occurs in 10-30% of cases. When it appears in the early postoperative period it is usually caused by lymphatic obstruction due to infection in the axilla. Late or secondary edema of the arm may develop years after radical mastectomy as a result of infection in the hand or arm with obliteration of lymphatic channels. After radical mastectomy the lymphatic drainage of the arm is always compromised and the extremity is more susceptible to infection from minor injuries than formerly. The patient should be warned of this and treatment instituted promptly if infection occurs. The management of well established chronic edema by elevation and elastic support is not very successful.

#### Prognosis.

Although the mean duration of life in untreated carcinoma of the breast is about 3 years, the course of the disease is highly variable; some untreated patients succumb

in 3 months, whereas others occasionally survive 5-10 years or longer.

The five-year clinical cure rate of all patients treated by radical mastectomy is 40-60%, and the local recurrence rate is about 15%. When there is no evidence of axillary or distant metastases at the time of operation, the five-year cure rate is 75-85%. When axillary metastases are present, the five-year cure rate is 35-50%. Operative mortality is about 1%.

The most unfavorable anatomic site for breast carcinoma is the medial portion of the inner lower quadrant. Breast cancer is probably more malignant in young than in old women, but the difference is not great.

The prognosis of carcinoma of the breast occurring during lactation or pregnancy is generally poor, since over one-fourth are inoperable, but when radical mastectomy is feasible the over-all five-year clinical cure rate in this group of patients is about 30%. The presence of axillary metastases in patients who are pregnant or lactating is an extremely poor prognostic sign.

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#### CARCINOMA OF THE MALE BREAST

Male breast cancer, since it is rare and usually asymptomatic, is often ignored by the patient and overlooked by the physician. It may occur at any time after age 20, but the peak incidence is in the fifties. The chief local finding is a painless mass not infrequently associated with nipple retraction, encrustation, or discharge. Treatment of operable cases is by radical mastectomy. The five-year survival rate is about 30% when the axillary nodes are involved and about 75% when they are not. Disseminated cancer of the male breast is usually well palliated by bilateral orchiectomy and estrogen therapy.

## CYSTIC DISEASE OF THE BREAST

### Essentials of Diagnosis

- Painful often multiple frequently bilateral masses in the breast
- Rapid fluctuation in size of mass is common
- Frequently pain occurs or increases and size increases during premenstrual phase of cycle
- Most common age is 30-50 Rare in postmenopausal women

Pain fluctuation in size and multiplicity of lesions help to differentiate these lesions from carcinoma and adenofibroma. Final diagnosis often depends on biopsy.

### General Considerations

Cystic disease is the most frequent lesion of the breast. It is common in women 30-50 years of age but rare in postmenopausal women which suggests that it may be related to ovarian activity. Estrogen hormone is considered an etiologic factor. The typical pathologic change in the breast is the formation of gross and microscopic cysts from the terminal ducts and acini. Large cysts are clinically palpable and may be several cm. or more in diameter.

### Clinical Findings

Cystic disease may produce an asymptomatic lump in the breast which is discovered by accident but pain or tenderness often calls attention to the mass. There may be discharge from the nipple. In many cases discomfort occurs or is increased during the premenstrual phase of the cycle at which time the cysts tend to enlarge rapidly. Fluctuation in size and rapid appearance or disappearance of a breast tumor are common in cystic disease. Multiple or bilateral masses are not unusual and many patients will give a past history of transient lump in the breast or cyclic breast pain. Pain fluctuation in size and multiplicity of lesions are the features most helpful in differentiation from carcinoma. However if skin retraction is present the diagnosis of cancer should be assumed until disproved by biopsy.

### Treatment

When cystic disease cannot be clearly distinguished from carcinoma on the basis of the clinical findings the patient should be prepared for radical mastectomy and the lesion explored in the operating room under

general anesthesia with provisions for immediate diagnosis by frozen section. Discrete cysts or small localized areas of cystic disease should be excised when cancer has been ruled out by microscopic examination. Surgery in cystic disease should be conservative since the primary objective of surgery is to exclude malignancy. Simple mastectomy or extensive removal of breast tissue is rarely if ever indicated.

When the diagnosis of cystic disease has been established by biopsy or is practically certain because the history is classical aspiration of a discrete mass is justifiable. The skin and overlying tissues are anesthetized by infiltration with 1% procaine and a No. 19 gauge needle is introduced. If a cyst is present typical watery fluid (straw-colored gray greenish brown or black) is easily evacuated and the mass disappears. The patient is re-examined at intervals of 2-4 weeks for 3 months and every 6 months thereafter through out life. If no fluid is obtained if a mass persists after aspiration or if at any time during follow up an atypical persistent lump is noted biopsy should be performed without delay. If a nipple discharge is present a smear should be taken for cytologic examination.

Breast pain associated with generalized cystic disease is best treated by avoidance of trauma and by wearing (night and day) a brassiere which gives good support and protection. Hormone therapy is not advisable because it does not cure the condition and has undesirable side effects.

### Prognosis

Exacerbations of pain tenderness and cyst formation may occur at any time until the menopause when the symptoms of cystic disease subside. The patient should be taught to examine her own breasts each month just after menstruation and to inform her physician if a mass appears.

Oberman H.A. & A.J. French. Chronic fibrocystic disease of the breast. *Surg Gynec & Obst* 112:647-52, 1961.

## FAT NECROSIS

Fat necrosis is a rare lesion of the breast but is of clinical importance because it produces a mass often accompanied by skin or nipple retraction which is indistinguishable from carcinoma. Trauma is presumed to be the cause although only about half of patients

give a history of injury to the breast. Ecchymosis is occasionally seen near the tumor. Tenderness may or may not be present. If untreated the mass associated with fat necrosis gradually disappears. As a rule the safest course is to obtain a biopsy. When carcinoma has been ruled out the area of involvement should be excised.

### BREAST ABSCESS

During nursing an area of redness, tenderness, and induration not infrequently develops in the breast. In the early stages the infection can often be reversed by discontinu-

ing nursing with that breast and administering a broad-spectrum antibiotic. If the lesion progresses to form a localized mass with increasing local and systemic signs of infection an abscess is present and should be drained.

A subareolar abscess may develop in young or middle-aged women who are not lactating. These infections tend to recur after incision and drainage unless the area is explored in a quiescent interval with excision of the involved collecting ducts at the base of the nipple.

Except for the subareolar type of abscess infection in the breast is very rare unless the patient is lactating. Therefore findings suggestive of abscess in the nonlactating breast require incision and biopsy of any indurated tissue.

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## Gynecology & Obstetrics

Ralph C. Benson

### COMMON GYNECOLOGIC DISORDERS

#### ABNORMAL UTERINE BLEEDING

Abnormal uterine bleeding means either (1) excessive or prolonged bleeding during the normal time of flow (hypermenorrhea, menorrhagia) or (2) any bleeding during the intermenstrual interval (metrorrhagia). Variation from her own norm is a matter of concern to almost every woman at some time between the menarche and the menopause.

Abnormal menstrual bleeding is always disturbing, often so severe as to be debilitating, and occasionally is a threat to life.

The causes of abnormal bleeding may be classified according to whether bleeding occurs during or between periods. Common causes of hypermenorrhea (menorrhagia) are myoma, endometrial polypoid, irregular shedding of the endometrium, functional hypertrophy of the uterus, blood dyscrasias and psychologic syndromes. Polymenorrhea (uterine bleeding which occurs more often than once every 24 days) may be due to a short cycle (proliferative phase less than 10 days, or secretory phase less than 14 days) or to premature interruption of the bleeding cycle due to physical or emotional stress. Metrorrhagia (irregular flow at times other than the normal menstrual period) may be due to hormonal imbalance or miscellaneous pelvic abnormalities. Hormonal causes include endometrial hyperplasia, ovulation bleeding ("mittelschmerz"), excessive administration of estrogens, anovulatory bleeding, and hypothyroidism. Pelvic abnormalities which cause metrorrhagia include cervical or endometrial polypoid, submucous myoma, carcinoma or sarcoma of the cervix, corpus uteri or fallopian tubes, and endometritis (postabortion, or due to tuberculosis or cervical stenosis).

#### Clinical Findings

**A Symptoms and Signs** The diagnosis of the disorders underlying the bleeding usually depends upon a careful description of the extent and amount of flow, related pain, if any, relationship to LMP and PMP, and a past history or family history of pertinent illnesses. All medications the patient has taken over the past month must be accounted for to rule out estrogenic stimulation or androgenic inhibition of flow. The following signs are significant: Fullness of the abdomen, cutaneous lesions, edema, exaggerated vascular patterns, herniation, tenderness or guarding of the abdomen, adenopathy, dullness or shifting dullness, and swelling, tenderness, or discharge in the vicinity of Skene's or Bartholin's glands. The rectovaginal examination may reveal tenderness, induration, nodulation, mass formation, and the presence of intraperitoneal fluid.

**B Laboratory Findings** Vaginal smears should be obtained (before digital examination) for cytologic and bacteriologic study. Vaginal smears taken during active bleeding and fixed in alcohol-ether can be laked of red cells (after fixation) with 1% HCl; the epithelial detritus which remains may reveal tumor cells or trophoblastic squamæ from a uterine abortion. In addition to urinalysis and routine hematocrit, STS, WBC and differential count, and sedimentation rate, blood studies (when necessary) should include bleeding time, clotting time, clot retraction time, platelet count, and a tourniquet test for capillary resistance. PBI and BEI tests are indicated to rule out abnormal thyroid function.

**C X-ray Findings** X-rays should be ordered only if tumors, fluid collections, or anatomic deformities are suspected, in which case a plain film of the abdomen, hysterosalpingography, cystography, and barium enema studies are indicated.

**D Special Examination** Biopsy and curettage are usually necessary to establish a

definitive diagnosis of the cause of bleeding. Polyps, tumors, and submucous fibrosis are commonly identified in this way. Cancer of the cervix or endometrium may require cone or four quadrant biopsy of the cervix and differential curettage of the cervix and uterus.

### Complications

Continued or excessive blood loss leads to anemia which favors local or systemic infection. Tumors may cause infertility. Cervical, uterine, or tubal neoplasm must be found and removed before metastasis occurs.

### Treatment

**A Emergency Measures** If bleeding has been massive, place the patient in the Trendelenburg position and give sedation. I.V. fluids and blood transfusions as required. Hemostasis is best achieved with surgical dilatation and curettage because this procedure has both therapeutic and diagnostic advantages. Temporary hemostasis (for 1-2 days) with diethylstilbestrol 25 mg orally every 15 minutes for 10 doses (or equivalent) is often desirable.

**B Curettage** Surgical curettage is the treatment of choice. After biopsy and curettage, hormonal therapy may be used for several months for the further control of bleeding.

### C Corrective Hormone Therapy

#### 1 Estrogens and progestogens -

(1) To control hypermenorrhea (not metrorrhagia) Progesterone aqueous suspension 35 mg I.M. on the 24th day after the onset of LMP, progesterone caproate (Delalutin®) 125 mg I.M. on the 21st day, norethindrone (Norlutin®) 10 mg orally daily for 7 days beginning on the 21st day, norethynodrel and ethinyl estradiol 3-methyl ether (Enovid®) 10 mg orally daily for 7 days beginning on the 21st day, medroxyprogesterone acetate (Provera®) 5 mg orally daily for 4 days beginning the 21st day.

(2) In metrorrhagia the following may be used: Estradiol valerate (Delestrogen®) 5 mg I.M. on the 14th day and progesterone caproate (Delalutin®) 250 mg I.M. on the 21st day, norethynodrel and ethinyl estradiol 3-methyl ether (Enovid®) 10 mg orally daily from the fifth through the 21st days.

**2 Androgens** - Androgen therapy is contraindicated in adolescent girls or young adult women because even minimal doses may cause permanent voice change and irreversible hirsutism. The following regimen may be used only in patients over 45 years of age: Testosterone enanthate (Delatestryl®) 200 mg

I.M., after 10 days methyltestosterone 10 mg sublingually daily for 2 weeks, after 7 days methyltestosterone 10 mg sublingually every other day for 3 weeks of each month for 2 months.

**3 Thyroid hormone** is indicated if it is certain that hypothyroidism is present and is the only cause of abnormal bleeding.

**4 Chorionic gonadotropin** 1000-2000 units I.M. daily for 12 days following ovulation will extend the postovulatory (luteal) phase and may thus enhance fertility.

**5 Cortisone** 25-50 mg orally daily for 2-3 months is of value in Stein-Leventhal syndrome but is not employed for hypermenorrhea or metrorrhagia due to other causes.

**D Irradiation Therapy** X-ray or radium therapy to terminate menses is indicated only for poor-risk or menopausal patients. In women under 35 years of age, about 1200 r will be required; in older women 800 r will usually suffice.

**E Surgical Therapy** Intractable bleeding, particularly in women over 40, may require hysterectomy. The ovaries should be preserved if they appear to be normal.

### Prognosis

In the absence of large tumors, pelvic inflammatory disease, and cancer, about 50% of patients with hypermenorrhea and almost 60% of patients with metrorrhagia will resume normal menstrual periods after curettage. Giving thyroid hormone or progesterone when indicated will increase these recoveries by 10-15%.

Goldfarb A.F. & M.L. Stone. Dysfunctional uterine bleeding during puberty. *Journal-Lancet* 28:521-4, 1958.

Woodruff, J.D., Prystowsky H. & R.W. Teindel. Postmenopausal bleeding: re-evaluation of old problem. *South M.J.* 51:302-5, 1958.

## POSTMENOPAUSAL VAGINAL BLEEDING

Vaginal bleeding which occurs 6 months or more following cessation of menstrual function may be due to local or systemic causes. Carcinoma of the cervix or endometrium accounts for 35-50% of cases. Administration of estrogens in excessive amounts or in noncyclic doses is the second most important cause.

Other causes include atrophic vaginitis, trauma, polyps, hypertensive cardiovascular disease, submucous myomas, trophic ulcers of the cervix associated with prolapse of the uterus, blood dyscrasias, and endogenous estrogen production by a feminizing ovarian tumor. Bleeding is usually painless, but pain will be present if the cervix is not patent, if bleeding is severe and rapid, or in the presence of infection or torsion of a tumor.

Bleeding varies from a bright ooze or brown discharge to frank hemorrhage. The patient may report a single episode of spotting or profuse bleeding for days or months. Laboratory examination may disclose exfoliated neoplastic cells, infection, or free basal cells and white cells (but no cornified epithelial cells). Passage of a sound into the uterus will demonstrate cervical stenosis and hematocolpos, will cause an intrauterine or endometrial neoplasm to bleed (Clark test), or may outline a cervical or uterine tumor. Aspiration biopsy or suction curettage often provides sufficient endometrial tissue for the purpose of examining for cancer, endometrial hyperplasia, endometritis, and other local disorders.

#### Treatment.

The patient should be hospitalized for thorough evaluation and definitive care. Dilatation and curettage (with polypectomy if indicated) will cure about half of all patients with postmenopausal bleeding. Withdraw all sex steroid drugs and do not reinstitute therapy until the cause of bleeding has been identified and bleeding has been controlled for at least 3 months. If bleeding recurs after a second curettage in a patient who is not taking estrogens, total hysterectomy and bilateral salpingo-oophorectomy may be indicated.

#### Prognosis

Curettage will cure many cases. The prognosis in women whose bleeding is due to severe neoplastic disease depends upon the extent of invasion and the success of antitumor therapy.

Israel, S. L., & L. L. Weber. Postmenopausal bleeding. *West J Surg* 64:515-9, 1956

## PRIMARY DYSMENORRHEA (Essential or Functional Dysmenorrhea)

### Essentials of Diagnosis

- Prodromal signs of breast engorgement, agitation, abdominal bloating, pelvic heaviness
- Intermittent aching or cramping in lower midline of abdomen at onset of bleeding
- Tenderness upon pelvic and abdominal examination

Although in most cases of dysmenorrhea there is no organic pathology (primary dysmenorrhea), a search should be made for organic causes such as cervical stenosis and endometriosis.

### General Considerations

Pain with menstrual periods for which no organic cause can be found (primary or essential dysmenorrhea) accounts for about 80% of cases of painful menses. The pain is almost always secondary to an emotional problem. Although primary dysmenorrhea is particularly common during adolescence, it may occur at any time from the menarche to the menopause. Dysmenorrhea and general menstrual discomfort are often described together as "menorrhagia."

### Clinical Findings.

Agitation, abdominal bloating, breast engorgement, and pelvic heaviness often precede dysmenorrhea. Intermittent aching to cramp-like discomfort in the lower midline usually accompanies the onset of bleeding. Circulatory engorgement of the vagina and cervix, slight patulousness of the os, and boggy feel of the uterus are frequently recorded before and during bleeding. Uterine, parametrial, and adnexal tenderness are often described as well.

Dysmenorrhea equivalents - periodic headache, diarrhea, tenaeness, urinary frequency and urgency - indicate monthly dysfunction of other organ systems.

### Differential Diagnosis.

Menstrual cramps which develop more than 5 years after the menarche are usually due to organic causes. Generalized abdominal pain or particularly well localized right- or left-sided pelvic pain are indicative of organic disease. Typical patterns of referred pain also suggest secondary dysmenorrhea.

## Treatment

**A Specific Measures** The definitive management of primary dysmenorrhea must be directed at the underlying psychodynamics. The gynecologist who is interested in these problems must be prepared to spend considerable time with the patient at each visit and to pursue a cure over a long period of time. Severe emotional disorders should receive specialized psychiatric attention.

**B General Measures** Analgesics are occasionally warranted until the diagnosis is established. The use of narcotics other than codeine should be avoided for fear of addiction. Warm douches may afford temporary relief. Diethylstilbestrol 0.5 mg orally daily for 14 days beginning with the first day of the period or methyltestosterone 5 mg orally 3 times daily from the fifth through the tenth days after the onset of menstruation (for 2 or 3 months) is a valuable temporary expedient. Methyltestosterone does not interfere with ovulation in this dosage.

**C Surgical Measures** Hysterectomy is never indicated.

## Prognosis

In women with insight who are cooperative and want to be cured, the prognosis is good. Very little can be done for the woman who prefers to use menstrual symptoms as a monthly refuge from responsibility and effort.

**Hayden G E** Relief of primary dysmenorrhea. An evaluation of the newer therapeutic agents. *Obst & Gynec* 16:730-3, 1960.

## DYSPAREUNIA

Dyspareunia (painful coitus) may be functional or organic or may be due to a combination of both causes. Either type may occur early (primary) or late (secondary) in marriage. The location of discomfort may be external (at the introitus) or internal (deep within the genital canal or beyond) and some women describe both types of pain.

External dyspareunia may be due to occlusive or rigid hymen, vaginal contracture due to any cause, or traumatic or inflammatory disorders of the vulva, vagina, urethra, or anus.

Organic causes of internal dyspareunia include hourglass contracture of the vagina,

septate vagina, severe cervicitis or retroposition of the uterus, prolapse or neoplastic disease of the uterus, tubo-ovarian disease, and pelvic endometriosis.

Pelvic examination often reveals marked contracture of the perineal and levator musculature with adduction of the muscles of the thighs, genital hypoplasia, and other congenital disorders, urethral caruncle, scarring or contracture of the vagina, vulvovaginitis, kraurosis vulvae, and rectal or bladder abnormality.

## Treatment

**A Specific Measures** Functional dyspareunia can only be treated by counseling and psychotherapy. Both partners should be interviewed. The treatment of organic dyspareunia depends upon the underlying cause.

**B General Measures** Mild sedation, e.g., phenobarbital 15 mg ( $\frac{1}{4}$  gr) orally t.i.d. or prochlorperazine (Compazine®) 15 mg orally daily, are of value for the relief of extreme emotional tension.

**C Local Measures** For functional dyspareunia, hymeneal-vaginal dilatations with a conical (Kelly) dilator or test tubes of graduated sizes may give relief. Anesthetic ointment applied to the introitus gives some relief but is of no permanent value. Organic dyspareunia due to vaginal dryness may be treated with a simple nongreasy ointment. Estrogen therapy is indicated for senile vulvovaginitis.

**D Surgical Measures** Hymenectomy, perineotomy, and similar plastic procedures should be performed only on clear indications. Significant vaginal obstructive lesions should be corrected. Treat chronic symptomatic cervicitis by cauterization or shallow conization.

## Prognosis

Few patients with functional dyspareunia are quickly and easily cured. Organic dyspareunia subsides promptly after elimination of the underlying cause of pain.

**Mears E** Dyspareunia. *Brit M J* 5093:443-5, 1958.

## LEUKORRHEA

Leukorrhea may occur at any age and affects almost all women at some time. It is

## Differential Diagnosis of the Causes of Leukorrhea

Color	Consistency	Amount	Odor	Probable Causes
Clear	Mucoid	+ to ++	None	Ovulation, excessive estrogen stimulation, emotional tension
Milky	Viscid	+ to +++	None to acrid	Cervicitis, Hemophilus vaginalis vaginitis
White	Thin with curd-like flecks	+ to ++	Fusty	Vaginal mycosis
Pink	Serous	+ to +++	None	Hypoestrogenism nonspecific infection
Yellow-green	Frothy	+ to +++	Fetid	Trichomonas vaginalis vaginitis
Brown	Watery	+ to ++	Musty	Vaginitis cervicitis Cervical stenosis endometritis salpingitis, neoplasm of the cervix, endometrium or tube Post-irradiational
Gray, blood-streaked	Thin	+ to ++++	Foul	Vaginal ulcer Pyogenic vaginitis-cervicitis (trauma, long-retained pessary forgotten tampon) Vaginal, cervical, endometrial, tubal neoplasm

not a disease but the manifestation of a local or systemic disorder. The most common cause is infection of the lower reproductive tract, other causes are inflammation of other areas, estrogenic or psychic stimulation, tumors, and estrogen depletion.

Leukorrheic discharge is usually white because of the presence of exfoliated or inflammatory cells. The persistence of some vaginal mucus is normal. Nevertheless, when soiling of the clothing or distressing local symptoms occur, the discharge must be considered abnormal.

### Clinical Findings.

**A. Symptoms.** Vaginal discharge, with or without discomfort, may be associated with itching when urine contaminates the inflamed introitus. The patient may complain of pudendal irritation, proctitis, vaginismus, and dyspareunia. There may be no symptoms.

**B. Laboratory Findings.** Blood findings may suggest low-grade infection. Cytologic study of a smear of vaginal secretion is indicated for all patients over 25 years of age or whenever malignancy is suspected. The same preparation can be stained to show trichomonads, Candida, or other organisms. Trichomonads are often seen in freshly voided urine contaminated with leukorrheic discharge if these organisms are noted in a catheterized specimen, urethral and bladder involvement by the flagellate is likely. Culture of the trichomonad is difficult but may be successful when Trichoseal<sup>®</sup> medium is used.

Leukorrhea associated with a positive serology may be due to syphilis, a positive

Frei test suggests lymphopathia venereum, the dmelcos skin test is positive in chancroid.

Inspect a fresh wet preparation of the vaginal fluid first for motile Trichomonas vaginalis. Look for heavy clouding of the spread and especially the covering of epithelial cells ("clue cells") by myriads of bacteria, these will probably be Hemophilus vaginalis. Then add 10% potassium hydroxide to take blood cells as an aid in visualization of Candida hyphae and spores. Examination of a gram-stained smear will identify intracellular gram-negative diplococci (Neisseria gonorrhoeae), other predominant bacteria, and helminths. If possible, culture the vaginal fluid anaerobically and aerobically to identify bacterial pathogens. Thioglycollate bacterial medium is most useful in the culture of Hemophilus microorganisms.

Inoculate Nickerson's, Sabouraud's, Pagano-Levin or a similar medium to demonstrate Candida.

Secure a vaginal smear for acid-fast staining and an inoculum for culture (or guinea pig inoculation) for Mycobacterium tuberculosis when tuberculosis is suspected.

### Prevention

The husband should use a condom if infection or reinfection is likely. Sexual promiscuity and borrowing of douche tips, underclothing, or other possibly contaminated articles should be avoided.

Tetracycline therapy over long periods of time may cause Candida vaginitis due to the overgrowth of these yeasts.



### Treatment.

**A Specific Measures** Treat infection with the specific drugs listed below. If sensitivity develops, discontinue medication and substitute another drug as soon as practicable. Continue treating the patient during menstrual flow. Choose a mode of therapy (e.g., suppositories, oral therapy) which need not be discontinued because of bleeding.

1 *Trichomonas vaginalis* vaginitis - It may be necessary to treat the patient during several menstrual periods, change the medication after 2-3 months in resistant cases. (1) Metronidazole (Flagyl<sup>®</sup>), \* 200 mg orally t i d for 7 days. Treat the husband similarly during the same interval. (Caution: This drug may encourage the growth of *Candida* organisms. Rapid disappearance of leukorrhea due in part to trichomoniasis may mask gonorrhea.) (2) Dihydroxyquinoline (Diodoquin<sup>®</sup>), dextrose, lactose, and boric acid (Floraquin<sup>®</sup>), carbarsone, or Devegan<sup>®</sup> suppositories, one vaginally twice daily for 8 weeks. Additional vaginal insufflation with the same preparation in powder form twice weekly for the first month is also helpful. (3) Furazolidone-nifuroxime (Tricofuron<sup>®</sup>) vaginal suppositories, one twice daily for 8 weeks.

2 *Candida albicans* - (1) Nystatin (Mycostatin<sup>®</sup>) vaginal suppositories, each containing 100,000 units, one daily for 2 weeks, is most effective. (2) Propionic acid gel (Propton Gel<sup>®</sup>), one application vaginally daily for 3 weeks. (3) Gentian violet, 2% aqueous solution applied topically to the vulva, vagina, and cervical area twice weekly for 3 weeks. (4) Gentian violet, lactic acid, and acetic acid (Gentia Jel<sup>®</sup>), one application vaginally daily for 3 weeks.

3 *Hemophilus vaginalis* vaginitis - (1) Sulfathiazole, sulfacetamide, and benzylsulfanilamide in cream form (Triple Sulf Cream<sup>®</sup>), one application daily for 2 weeks. (2) Acidiflox 0.1% hexetidine gel (Sterisil<sup>®</sup>), one application daily for 2 weeks.

4 Atrophic (senile) vaginitis - (1) Diethylstilbestrol, 0.5 mg vaginal suppository, one every third day for 3 weeks. Omit medication for one week (to avoid uterine bleeding) then resume cyclic therapy indefinitely unless contraindicated. (2) Dienestrol vaginal cream, one-third applicator-full every third day for 3 weeks. Omit medication for one week, then resume cyclic therapy. (3) Diethylstilbestrol, 0.2-0.5 mg (or equivalent), orally daily for 3 weeks each month.

5 Gonorrheal vaginitis - Treat as directed in Chapter 20. Caution: Treatment will be inadequate unless 3 sets of slides, or preferably, cultures of discharge from Skene's ducts and

the cervical canal reveal no gonococci. Perform a serologic test for syphilis prior to treatment and repeat 2 months later.

**B General Measures** Utilize internal menstrual tampons to reduce vulvar soiling, pruritus, and odor. Coitus should be avoided until a cure has been achieved. Trichomonal and candidal infections require treatment of the husband also. Relapses are often reinfections. Re-treat both parties.

Antipruritic medications are disappointing unless an allergy is present. Specific and local therapy will usually control itching promptly.

**C Local Measures** Occasional acetic douches (2 Tbsp of vinegar per L of water) may be beneficial in the treatment of leukorrhea. Caution: Never use alkaline (soda) douches. They are unphysiologic and often harmful because they discourage the normal vaginal flora by reducing vaginal pH.

Douches are not essential to cleanliness or marital hygiene. Too-frequent douches of any kind tend to increase mucus secretion. Irritating medications cause further mucus production.

In severe, resistant or recurrent trichomonal or candidal vaginitis, treat the cervix (even when it is apparently normal) by chemical or light thermal cauterization. Investigate the urinary tract and Skene's and Bartholin's ducts and treat these areas if they appear to be reservoirs of reinfection.

**D Surgical Measures** Hospital cauterization, conization of the cervix, incision of Skene's glands, or bartholinectomy may be required. Cervical, uterine or tubal disease (tumors, infection) may necessitate laparotomy, irradiation, or other appropriate measures.

### Prognosis

Leukorrhea in pregnant, debilitated, or diabetic women is difficult to cure, especially when due to *Trichomonas vaginalis*, *Candida albicans* or *Hemophilus vaginalis*. Repeated or even continuous treatment over 3-4 months may be required until the patient is delivered or the diabetes is controlled.

The prognosis is good if the exact diagnosis is made promptly and intensive therapy instituted. Treatment of only one of several causes may be the reason for failure of therapy.

Heltal, A. Hemophilus vaginitis and nonspecific vaginitis. *Ann New York Acad Sc* 83:290-3, 1959.

Nathanson, E. A. Treatment of vaginal candidiasis. *Obst & Gynec* 16:601-4, 1960.

\*See p. 807 for a comment on the status of this drug --Ed

Patyson, R. A.: Trichomoniasis and candidiasis vulvovaginitis. Procedures that most frequently result in permanent cures and prevent thrush in the newborn. *New York J. Med.* 60:3825-9, 1960.

### CYST & ABSCESS OF BARTHOLIN'S DUCT & GLAND

Gonorrhea and other infections often involve Bartholin's duct and, to a lesser degree, the gland itself. Obstruction prevents drainage of secretions and exudations, which leads to pain and swelling. The infection resolves and pain disappears, but distention of the duct persists. Reinfection causes recurrent tenderness and further enlargement of the duct.

The principal symptoms are periodic painful swelling on either side of the introitus and dyspareunia. Fullness in one or both of the labia and soft distortion of the introitus are apparent. A fluctuant swelling 1-4 cm. in diameter in the inferior portion of either labium minus is a sign of occlusion of Bartholin's duct. Tenderness is evidence of active infection.

Differentiate from inclusion cysts (after laceration or episiotomy), large sebaceous cysts, hydradenoma, congenital anomalies, and cancer of Bartholin's gland or duct (rare).

Treat infection with broad-spectrum antibiotics and local heat. If an abscess develops, incise and drain. After the acute process has subsided, marsupialize the affected duct or excise the duct and gland.

The prognosis is uniformly excellent.

Jacobson, P.: Marsupialization of vulvovaginal (Bartholin) cysts. Report of 140 patients with 152 cysts. *Am. J. Obst. & Gynec.* 79:73-9, 1960.

### URETHRAL CARUNCLE

Urethral caruncles may occur at any age, but postmenopausal women are most commonly affected. Caruncle may be due to infection, ectropion, papilloma, angioma, or benign or malignant neoplasms. Most caruncles represent eversion of the urethral mucosa or bacterial infections at the meatus (or both). Suspect cancer when the lesion is persistent and progressive.

Dysuria, frequency, tenderness, vaginal bleeding, leukorrhea, and dyspareunia are the

usual complaints, but a few caruncles are asymptomatic. A small, bright red tumor or sessile mass protruding from the urethral meatus may bleed, exude, or cause pain depending upon its etiology and size.

Complications include local ulceration, urethritis, and vaginitis. Bleeding is rarely excessive. An occasional caruncle may represent malignant change in a granuloma or may be a primary urethral or vulvar cancer.

### Treatment.

Obtain tissue for biopsy and exudate for smear and culture. If the growth is benign and infection is minimal, fulgurate lightly under topical anesthesia and apply nitrofurazone (Furacin®) cream or other chemotherapeutic agent. Repeated light fulguration is preferred to extensive coagulation initially. A bladder sedative compound (see p. 397) will usually relieve urinary distress. Excision may also be a valuable procedure, but care must be taken to avoid causing stenosis of the urethra. Local or systemic cyclic estrogen therapy is helpful before and after treatment in the postmenopausal patient. The prognosis in benign cases is excellent.

If the growth is malignant, the patient should be referred for radical surgery or irradiation therapy.

Garake, G. L.: The female urethra. *Minnesota Med.* 41:452-9, 1958.

### CARCINOMA OF THE CERVIX

#### Essentials of Diagnosis.

- Abnormal uterine bleeding and vaginal discharge.
- Cervical lesion may be visible on inspection as a mass or ulceration.
- Vaginal cytology usually positive; must be confirmed by biopsy.

Abnormal bleeding and vaginal discharge are also found in cervicitis, venereal cervical lesions, and cervical polyps. A visible suspicious cervical lesion may be found in benign cervical polyps, cervical ulceration, nabothian cyst, cervical endometriosis, and cervical tuberculosis.

#### General Considerations.

Cancer of the cervix is the second most common malignancy in women. Squamous cell cancer accounts for about 85% of cases; adenocarcinoma accounts for almost 5%.

Cancer appears first in the intra-epithelial layers (the preinvasive stage, or carcinoma in situ). Preinvasive cancer is a common diagnosis in women 30-40 years of age, but most patients with invasive carcinoma are 40-50 years old. Five to 10 years probably are thus required for carcinoma to penetrate the basement membrane and invade the tissues in most instances. After invasion death usually occurs in 3-5 years in the untreated patient.

Invasion is associated with ulceration and spotting. Sanguineous vaginal discharge or abnormal bleeding does not occur until the cancer has penetrated into the substance of the cervix.

### Clinical Findings

**A Symptoms and Signs** The most common findings are metrorrhagia and cervical ulceration. Hypermenorrhea occurs later. Leukorrhea (sanguineous or purulent, odorous, and nonpruritic) appears after the invasive stage. Vesical and rectal dysfunction or fistulas are late symptoms. Pain also occurs late. Anemia, anorexia, and weight loss are signs of advanced disease.

Cervical carcinoma in situ is not visible unless one employs the colposcope. Occasionally a small patch of leukoplakia may represent preinvasive carcinoma, or a thickened area in an everted cervix may show malignant change. Biopsy or conization of the cervix is required for diagnosis.

**B "Staging" or Estimate of Gross Spread of Cancer of the Cervix** The depth of penetration of the malignant cells beyond the basement membrane is a reliable clinical guide to the extent of primary cancer within the cervix and the likelihood of secondary or metastatic cancer. It is customary to stage cancers of cervix as follows (Percentages given are approximations).

- Stage 0 Preinvasive, or carcinoma in situ
- Stage I Carcinoma confined to the cervix (11% have lymph node metastases)
- Stage II Carcinoma extending beyond the cervix to invade the upper two-thirds of the vagina or the parametrial tissues but without spread to the pelvic wall (22% have lymph node metastases)
- Stage III Carcinoma extending to the pelvic wall or the lower third of the vagina (33% have lymph node metastases)
- Stage IV Carcinoma involving the bladder or rectum (or both) or which has extended beyond the limits of stage III (77% have lymph node metastases)

### C Laboratory Findings

**1 Schiller test** - Aqueous solutions of iodine stain the surface of the normal cervix mahogany-brown because normal cervical epithelial cells contain glycogen. Zones of cancer within the epithelium over the cervix do not contain glycogen and so fail to stain with Lugol's or Schiller's iodine reagent. Scaras, areas of erosion or erosion cystic mucus glands and zones of nonmalignant leukoplakia also fail to take the stain, however, and so this test is useful only in identifying abnormal areas.

**2 Cytologic examination (Papanicolaou) - Vaginal cytology is usually positive.** If the smear is negative but cancer is still suspected, biopsy is required. Biopsy confirmation of a positive cytologic examination is always required before definitive treatment is given. Vaginal smears for cytologic examination should be prepared as requested by the pathologist who will examine the slides. A frequently used technique is as follows.

The patient should not have douches for 24 hours or more before the examination and should not have bathed for several hours. Smears obtained during bleeding episodes are less desirable than those secured at other times.

Insert a thick-walled glass pipet with a rubber suction bulb into the posterior vaginal fornix and aspirate fluid. Blow the fluid onto 2 or 3 slides and gently spread it over the slides with the pipet. The smear should be thicker than a standard blood smear but not so thick as to be opaque. An irregular distribution is not objectionable. Smears may also be made from material collected in a speculum and transferred directly to the slide with a clean gloved finger. A cotton applicator moistened with water can be used but the mucus must be rolled onto the slide for a good preparation. Scrapings, especially of a lesion of the cervix, may be obtained with a wooden tongue blade.

**Fix immediately before drying** by placing the slides in an equal mixture of ethyl ether and 95% ethyl alcohol. Even a slight amount of drying can impair the staining quality of the cells.

Keep the slide surfaces separated by attaching paper clips to the upper edges of alternate slides.

After fixation for one hour, the slides are removed and allowed to dry. These dry slides will retain their staining qualities for as long as 2 weeks. Glycerin need not be applied as a preservative.

If a serial study is desired, most patients can learn to aspirate, smear, and fix their own slides.

An excess of exudate can be dropped into Boulin's or Zenker's fixative (10% formalin causes too much shrinkage) and subsequently treated as a "button" for sectioning. The following information should be included with the request for cytologic examination: Patient's name, date, record of previous vaginal smear (Yes or No, Positive or Negative), age, marital status, gynecologic complaints, menstrual history, LMP, operations, endocrine treatments, x-ray or radium treatments, provisional diagnosis, and purpose of study.

The results of the microscopic examination are reported as follows:

- Type I = Negative for malignant cells
- Type II = Negative for malignant cells but contains atypical benign elements (including those with changes due to radiation)
- Type III = Markedly atypical cells suggestive of malignancy
- Type IV = Probably malignant cells
- Type V = Cells cytologically conclusive of malignancy

**Note:** Vaginal cytology never yields a positive diagnosis of cancer; direct tissue examination (biopsy, curettage) is required for confirmation before definitive therapy is given.

**D X-ray Findings:** Chest and bone x-rays may reveal metastases in advanced disease.

### Complications.

Metastases to regional lymph nodes occur with increasing frequency from stage I to stage IV. Paracervical extension occurs in all directions from the cervix. The ureters are often obstructed lateral to the cervix, causing hydronephrosis and hydronephrosis and consequently impaired kidney function. Almost two-thirds of patients with carcinoma of the cervix die of uremia when ureteral obstruction is bilateral. Pain in the back and in the distribution of the lumbosacral plexus is often indicative of neurologic involvement.

Pelvic infections which complicate cervical carcinoma are most often due to streptococci and staphylococci.

Vaginal fistulas to the gastrointestinal and urinary tracts are severe late complications. Incontinence of urine and feces are major complications, particularly in debilitated individuals.

Hemorrhage is the cause of death in 10-20% of patients with extensive invasive carcinoma of the cervix.

### Prevention

Avoidance of cervical trauma and prompt care of vaginitis and cervicitis will probably reduce the incidence of cervical cancer. Periodic examination of women (including vaginal cytology) will disclose cancerous changes before symptoms develop. The earlier the stage at which cancer is found, the better the prognosis.

### Treatment.

**A Emergency Measures:** Vaginal hemorrhage originates from gross ulceration and cavitation in stage II-IV cervical carcinoma. Ligation and suturing are usually not feasible, but ligation of the uterine or hypogastric arteries may be life-saving when other measures fail. Styptics such as Negatan<sup>®</sup>, 10% silver nitrate solution and acetone are effective, although delayed sloughing may result in further bleeding. Vaginal packing is helpful.

**B Specific Measures:** Irradiation (by a specialist) is generally the best treatment for invasive carcinoma of the cervix. The objectives of irradiation treatment are (1) the destruction of primary and secondary carcinomas within the pelvis and (2) the preservation of tissues not invaded. Gamma emissions derived from x-rays, cobalt<sup>60</sup>, radium, the cyclotron, the linear accelerator, and similar sources are employed. All stages of cancer may be treated by this method and there are fewer medical contraindications to irradiation than to radical surgery. Optimal results have been achieved with externally applied roentgen therapy combined with intracavitary and paracervical vaginal radium therapy.

### Prognosis

The over-all five-year arrest rate is about 45% in the best clinics. Percentage arrest rates are inversely proportionate to the stage of the cancer: stage 0, 99%, stage II, 65%, stage III, 25%, stage IV, 5%.

Johnson, L. D. Role of the obstetrician in the prevention of cervical cancer. *New England J Med* 262:1297-1301, 1960.

Lock, A. R., Greiss, F. C., & I. Blake. Stage I carcinoma of the uterine cervix. Comparison of results with variations in treatment. *Am J Obst & Gynec* 80:984-96, 1960.

Preventing cancer of the uterine cervix. *Brit. M. J.* 5295:1817-8, 1962.

## CARCINOMA OF THE ENDOMETRIUM (Corpus or Fundal Cancer)

Adenocarcinoma of the endometrium is the second most common malignancy of the female genital tract. It occurs with greatest frequency in women 60-70 years of age. Abnormal uterine bleeding is the presenting sign in 80% of cases. A watery, serous or sanguineous, malodorous vaginal discharge is occasionally present. Pyometra or hematometra may be due to carcinoma of the endometrium. Pain occurs late in the disease or when the uterus becomes infected.

Surgical dilatation and curettage and pathologic examination of curettings is the most reliable means of diagnosis. Cytologic examination of aspirated material from the upper endocervical canal is diagnostic in 80-85% of cases.

The Clark test is performed by gently passing a blunt curved uterine sound through the endocervical os and into the uterine cavity, and then removing it without further manipulation. Bleeding constitutes a positive test, and is presumptive evidence of fundal cancer. However, benign polyps, submucous myomas, and even an early pregnancy may also cause bleeding. Tissue is therefore required to make the diagnosis of cancer. Hysteroscopy shows hypertrophic folds of endometrium, an irregular bulky tumor tending to fill the cavity, or gross papillary excrescences within the cavity.

### Prevention.

Routine screening of all women by periodic vaginal smears and prompt dilatation and curettage of patients who report abnormal menstrual bleeding or postmenopausal uterine bleeding will uncover many incipient as well as clinical cases of endometrial cancer.

### Treatment.

**A. General Measures** Patients with carcinoma of the uterus are often weak, anemic, diabetic, or hypertensive; they should be restored to maximum health before surgery.

**B. Specific Measures** Treatment usually consists of total hysterectomy and bilateral salpingo-oophorectomy. Preliminary intracavitary radium therapy is probably indicated if the cancer is poorly differentiated or if the uterus is definitely enlarged in the absence of myomas.

### Prognosis.

With early diagnosis and treatment, the five-year cure rate is 80-85%.

Müller, N.F.: Carcinoma of the endometrium. Some facts, figures, and fancies. *Obst. & Gynec.* 15:579-86, 1960.  
Toombley, G.H., & W.E. Jacobowitz: Carcinoma of the endometrium. New York J. Med. 62:2194-9, 1962.

## CERVICAL POLYPS

Cervical polypoidosis is a common disorder which may occur at any time after the menopause but which is only occasionally noted in postmenopausal women. The cause is not known, but inflammation may play a role in etiology. The principal symptoms are leukorrhea and abnormal vaginal bleeding. A cervical polyp is visible on pelvic examination unless it is high in the canal, in which case hysterosalpingography or sounding of the cervix may be necessary. Vaginal cytologic examination demonstrates infection and metaplasia (abnormal cells of stage II or III, if present).

Cervical polyp must be differentiated from neoplastic disease of the endometrium, small submucous pedunculated myoma, endometrial polyp, and the products of an aborted conception.

### Treatment.

**A. Medical Measures** Cervical discharge should be submitted for culture and sensitivity tests and antibiotic therapy instituted as indicated.

**B. All cervical polyps should be removed surgically.** They can often be removed in the office by avulsion, scalpel excision, or high-frequency electrosurgery. All tissue recovered should be examined by a pathologist to rule out malignant change. If the cervix is soft, patulous, or definitely dilated and the polyp is large, surgical dilatation and curettage in a hospital is required (especially if the pedicle is not readily visible). Exploration of the cervical and uterine cavities with the polyp forceps and curette may reveal multiple polyps or other important lesions. Warm acetic acid douches are indicated after removal to reduce the inflammatory reaction.

### Prognosis.

Simple removal is almost always curative. All polyps should be examined carefully for evidence of malignancy.

Goforth, J.L.: Polyps and papillomas of the cervix uteri. *Texas J. Med.* 49:81-6, 1953

Woodruff, V D., & W.F. Peterson: *Condylomata acuminata of cervix* Am J Obst & Gynec 75 1354-62. 1958

## MYOMA OF THE UTERUS (Fibroid Tumor, Fibromyoma)

### Essentials of Diagnosis

- Irregular enlargement of the uterus (may be asymptomatic)
- Hypermenorrhea, metrorrhagia, dysmenorrhea, and leukorrhea (variable)
- Acute and recurrent pelvic pain if the tumor becomes twisted on its stalk
- Symptoms due to pressure on neighboring organs (large tumors)
- X-ray evidence of calcification of some degenerative myomas

The irregular enlargement of the uterus observed with myomas must be differentiated from the similar but regular enlargement that may occur with uterine pregnancy, adenomyosis, benign uterine hypertrophy, and adherent adnexa or viscera. Uterine bleeding, dysmenorrhea, and leukorrhea may also occur with other types of neoplastic disease, cervicitis, cervical stenosis, and other gynecologic disorders. These possibilities must be considered even when the diagnosis of myoma has been established.

### General Considerations

Myoma is the most common neoplasm of the female genital tract. It is a discrete, round, firm benign uterine tumor composed of smooth muscle and connective tissue. At least 10% of all disorders of women are related to myoma. Only 2% are solitary, and several hundred have been found in one uterus. Some myomas become quite large, the largest on record weighed over 45.5 Kg (100 lb). The most convenient classification is according to anatomic location: (1) intramural, (2) submucous, (3) subserous, (4) intraligamentous, (5) parasitic, i.e., deriving its blood supply from an organ to which it becomes attached, and (6) cervical.

### Clinical Findings.

A. Symptoms and Signs. Intramural, subserous, and intraligamentary tumors may distort or obstruct neighboring viscera, causing pain and bleeding. Submucous myomas which

become large enough to displace adjacent organs cause dysmenorrhea, leukorrhea, hypermenorrhea, and metrorrhagia. Cervical myomas cause vaginal discharge, bleeding, dyspareunia, and infertility. Parasitic myomas cause intestinal obstruction if they are large enough to involve the omentum or bowel.

In nonpregnant women the manifestations of myoma are often minimal, e.g., pelvic pressure or distention, urinary frequency, menometrorrhagia, constipation, dysmenorrhea, and retention cysts. Infertility may be due to a myoma which obstructs or distorts the genital tract.

In pregnant women myomas cause additional hazards: abortion, malpresentation, failure of engagement, premature labor, pain, dystocia, desultory labor, and postpartum hemorrhage.

B. X-ray Findings. A flat film of the pelvis may demonstrate opacities if calcific degeneration has occurred. Hystero-graphy (contraindicated during pregnancy) may reveal a cervical or submucous tumor.

C. Special Examinations. In the nonpregnant woman vaginal examination under general anesthesia and surgical dilatation and curettage can be used in doubtful cases to establish the diagnosis.

### Treatment.

A. Emergency Measures. Give blood transfusions as indicated. Emergency surgery is required for acute torsion of a pedunculated myoma or intestinal obstruction. The only emergency indication for myomectomy during pregnancy is torsion; abortion is not inevitable, but hormones are of no value in prevention of miscarriage.

### B. Specific Measures

1. Nonpregnant women - In nonpregnant women, small asymptomatic myomas should be left undisturbed and observed at intervals of 6 months. Intramural and subserous myomas do not require surgery unless they are larger than a 14 week pregnancy, multiple, or distorting. Cervical myomas should be removed when they become larger than 3-4 cm in diameter.

2. Pregnant patients - If the uterus is no larger than a 6 month pregnancy by the fourth month of gestation, an uncomplicated course can be anticipated. If the mass (especially a cervical tumor) is the size of a 5 or 6 month pregnancy by the second month of gestation, abortion will probably occur. Wherever possible, defer surgery until 6 months after de-

livery, at which time involution of the uterus and regression of the tumor will be complete

**C. Surgical Measures:** The surgical measures available for the treatment of myoma are myomectomy, total or subtotal abdominal or vaginal hysterectomy, and, if surgery is contraindicated, irradiation. The ovaries should be preserved if possible. Subtotal vaginal hysterectomy has been virtually abandoned because it is a difficult procedure and there is no great advantage to not removing the cervix. Radium should not be used for submucous tumors. Myomectomy is the treatment of choice during the childbearing years

#### Prognosis.

Surgical therapy is curative. Future pregnancies are not endangered by myomectomy, although cesarean delivery may be necessary. Careful hysterectomy with retention of normal ovaries does not hasten menopause

Bell, H.G., & H. Edgehill: Sarcomas developing in uterine fibroids. Review of the literature and presentation of three cases. *Am. J. Surg.* 100:416-22, 1960.

Radman, H.M.: Conservative treatment of fibromyomas in women of the childbearing age. *J. Mt. Sinai Hosp.* 9:181-7, 1960

## ENDOMETRIOSIS & ADENOMYOSIS

#### Essentials of Diagnosis.

- Abnormal uterine bleeding and rectal bleeding.
- Dysmenorrhea,
- Dyspareunia and painful defecation before menses, progressing in severity during menses

Differentiate from other causes of abnormal vaginal and uterine bleeding. If indurated nodules are not tender, consider neoplasm. Tender indurated nodules are not present in primary dysmenorrhea.

#### General Considerations.

Aberrant growth of endometrium outside the uterine cavity (endometriosis) and benign invasion of endometrium into the uterine musculature (adenomyosis) are common causes of abnormal uterine bleeding and dysmenorrhea. Endometriosis frequently causes dyspareunia, painful defecation, and rectal bleeding. The pain tends to be constant, beginning 2-7 days

before the onset of menses and becoming increasingly severe until flow slackens. Pelvic examination discloses tender indurated nodules, especially if the examination is done at the onset of menstruation

Endometriosis and adenomyosis must be distinguished from pelvic inflammatory disease (differentiated by the presence of fever and leukocytosis), and from tuberculosis, myomatosis, and neoplasia of the reproductive organs, in none of which disorders are the symptoms aggravated by menstruation. Bowel invasion by endometrial tissue may produce clinical findings which are almost indistinguishable from bowel neoplasm; differentiation in these rare instances depends upon biopsy. Dilatation and curettage will generally distinguish adenomyosis from submucous myoma and cancer of the endometrium.

Laboratory findings are of no value in the diagnosis of these disorders. Barium contrast studies are helpful in the delineation of colonic involvement in endometriosis, and contrast hystero-graphy is diagnostic in adenomyosis if the medium penetrates the glands

Endometriosis is a significant cause of infertility

#### Treatment.

##### A Endometriosis

1 Medical treatment - Young married women with mild but advancing endometriosis should be advised to become pregnant without delay to secure a family and retard the progress of the disease. If the patient does not want a child or cannot become pregnant, exogenous hormone therapy is indicated with one of the following regimens

(1) Progestins, e.g., norethynodrel and ethinyl estradiol 3-methyl ether (Enovid®), 10 mg orally daily for 2 weeks beginning on the fifth day of the menstrual period and increasing by 10 mg increments every 2 weeks until 40 mg. daily are being taken. Continue for 6-9 months for optimal effect. This drug induces pseudopregnancy. Restrict sodium during administration of Enovid® to prevent fluid retention. If fluid does accumulate, give hydrochlorothiazide (Hydro-Diuril®), 50 mg orally every third day.

(2) Diethylstilbestrol, 1 mg. orally on the first day of the menstrual period and increasing by 1 mg. increments every 3 days until 5 mg. have been given. Then give 25 mg daily, increasing by 25 mg. increments every week until 100 mg. are being taken daily. Continue 100 mg. daily for 4 months, decrease by 25 mg. weekly to a daily dose of 5 mg. daily over the next 2 months, and then give 1 mg. daily for one month, and stop. This regimen

usually relieves symptoms completely, but about 30% of patients have recurrences when medication is withdrawn.

(3) Methyltestosterone, 5-10 mg. sublingually daily, usually relieves pain and retards the growth of endometrial tissue. Ovulation is usually not impaired by the smaller dose, and many patients on androgen therapy become pregnant. Medication must be discontinued at the first signs of virilization, since voice changes induced by androgen therapy are not reversible.

Analgesics with codeine may be given as necessary for pain.

2 Surgical measures - The surgical treatment of moderately extensive endometriosis depends upon the patient's age and her desire to preserve reproductive function. If the patient is under 35, resect the lesions, free adhesions, and suspend the uterus. About 20% of patients so treated will become pregnant, although half must undergo surgery again when the disease progresses. If the patient is over 35 years old and both ovaries are involved, both ovaries, the tubes, and the uterus must be excised. If one ovary is normal, it need not be removed.

Extensive endometriosis almost invariably necessitates ablation of both ovaries and tubes and the uterus regardless of the patient's age, unless it is possible to improve the patient's condition by inducing pseudopregnancy with progestins (see above) so that a less radical procedure will suffice.

3 X-ray therapy - If surgery is contraindicated or refused, castration doses of x-ray will relieve the symptoms and cause almost complete regression of the lesions. X-ray therapy cannot be condoned unless the diagnosis of far-advanced endometriosis is unequivocal.

B. Adenomyosis. The only treatment is surgical. Hysterectomy is the treatment of choice because en bloc excision is required unless a capsule or distinct margin of involvement is found at operation. Normal ovaries should be retained. X-ray or radium irradiation is therapeutically effective but should rarely be used in women under 40 because it induces menopause.

### Prognosis

The prognosis for reproductive function in early or moderately advanced endometriosis is good with conservative therapy. Castration is curative in severe and extensive endometriosis; if it is refused, hormone therapy may be tried.

Complete relief of symptoms is the rule following corrective surgery for adenomyosis.

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## MALPOSITION OF THE UTERUS ("Tipped Uterus")

Various types of uterine malposition have been said to cause pelvic pain, backache, abnormal uterine bleeding, and infertility. However, current opinion holds that a relationship between malposition of the uterus and definite symptomatology can be established only after prolonged and critical evaluation. Back pain, for example, is usually due to an orthopedic disorder. Antelexion of the uterus almost never causes symptoms and seldom requires treatment. Lateral displacements of the uterus are frequently due to far more serious pelvic disease (usually neoplasms). Retrodisplacements may cause symptoms and require treatment, but the symptomatology itself is of little use in diagnosis.

The diagnosis of any type of uterine malposition depends upon abdominal and rectovaginal examination, and can be confirmed and documented by hystero-graphy. If a woman complaining of pain, bleeding, or infertility is found to have a retroverted or retroflexed uterus and if other more common causes of these complaints have been ruled out, a trial of pessary support is warranted. If the pessary consistently relieves symptoms and the symptoms return when the pessary is removed, it may be advisable to suspend the uterus surgically. If surgery is contraindicated or refused, the pessary may be worn intermittently until the menopause, at which time regression of uterine tissue will probably relieve symptoms altogether.

Knee-chest exercises are of doubtful value.

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 Youssef, A.T.: New technique (surgical) for correction of retroversion-flexion of the uterus by vaginal route. *J. Obst. & Gynaec. Brit. Emp.* 67:485-9, 1960.



## UTERINE PROLAPSE (DESCENSUS)

Uterine prolapse most commonly occurs as a delayed result of childbirth injury to the pelvic floor (particularly the transverse cervical and uterosacral ligaments). Unrepaired lacerations of the levator musculature and perineal body aggravate the weakness. Attenuation of the pelvic structures with aging, congenital weakness, neurologic injury to the sacral nerves, ascites, and internal genital tumors accelerate the development of prolapse.

Retroposition of the uterus usually develops with prolapse, whereupon the corpus, now in the axis of the vagina, exerts a piston-like action with each episode of increased intra-abdominal pressure. For unknown reasons the cervix often becomes elongated.

In slight prolapse the uterus descends only part way down the vagina. In moderate prolapse the corpus descends to the introitus and the cervix protrudes slightly beyond. In marked prolapse (procidentia) the entire cervix and uterus protrude beyond the introitus and the vagina is inverted.

### Clinical Findings

A firm mass is palpable in the lower vagina. In moderate prolapse the cervix protrudes beyond the introitus. The patient complains of a sense of heaviness in the pelvis, low backache, and a "dragging" sensation in the groin.

Pelvic examination with the patient bearing down or straining in the supine or standing position will demonstrate downward displacement of a prolapsing cervix and uterus. Herniation of the bladder, rectum, or cul-de-sac is diagnosed in a similar way. Note uterine or adnexal neoplasms and ascites as possible causes of prolapse.

Rectovaginal examination may reveal rectal fullness (rectocele) or hernia of the pouch of Douglas behind and below the cervix. A metal sound or firm catheter within the bladder may be used to determine the extent of cystocele.

### Differential Diagnosis

Prolapse of the uterus must be differentiated from tumors of the cervix and fecal impaction in a rectocele.

### Complications

Abnormal uterine bleeding and abortion may result from disordered uterine circulation. Ulceration in procidentia predisposes to cancer.

### Prevention

Avoidance of obstetric trauma, and postpartum exercises to strengthen the levator musculature (Kegel), will prevent or minimize subsequent prolapse. Prolonged cyclic estrogen therapy for the postmenopausal woman will often conserve the strength and tone of the pelvic floor.

### Treatment

Selection of the surgical approach depends upon the patient's age, the extent of prolapse, and her desire for menstruation, pregnancy, and coitus. Uterine suspension or ventrofixation is not effective in the treatment of prolapse.

Palliative therapy with a well-fitted pessary (e.g., inflatable doughnut type, Gellhorn pessary) may give relief if surgery is refused or contraindicated.

### Prognosis

Prolapse may remain constant for months or years, but it never regresses and will ultimately become more extreme unless corrected surgically.

## OVARIAN TUMORS

### Follicle (Retention) Cysts

Follicle cysts are common, frequently bilateral and multiple cysts which appear on the surface of the ovaries as pale blebs filled with a clear fluid. They vary in size from microscopic to 4 cm. in diameter (rarely larger). These cysts represent the failure of an incompletely developed follicle to reabsorb. They are commonly found in prolapsed adherent ovaries or when a thickened previously inflamed ovarian capsule prevents extrusion of the ovum. Symptoms are usually not present unless torsion or rupture with hemorrhage occurs, in which case the symptoms and signs of an acute abdomen are often present. Large or numerous cysts may cause aching pelvic pain, dyspareunia, and occasionally abnormal uterine bleeding. The ovary may be slightly enlarged and tender to palpation, and the vaginal smear will often show a high estrogen level and a lack of progesterone stimulation.

Pelvic inflammatory disease and endometriosis must be considered in the differential diagnosis.

Most follicle cysts disappear spontaneously within 60 days without any treatment, when symptoms are disturbing, warm douches, pel-

vic diathermy, and reestablishment of ovulation with progesterone medication may be helpful. Malignant change does not occur.

Any cyst which becomes larger than 5 cm in diameter or which persists longer than 60 days probably is not a follicle cyst.

#### Corpus Luteum Cysts.

Corpus luteum cysts are functional, non-neoplastic enlargements of the ovary caused by the unexplained increase in secretion of fluid by the corpus luteum which occurs after ovulation or during early pregnancy. They are 4-6 cm in diameter, raised, and brown, and are filled with brown serous fluid. A contracted blood clot is often found within the cavity.

Corpus luteum cysts may cause local pain and tenderness, and either amenorrhea or delayed menstruation followed by brisk bleeding after resolution of the cyst. They are usually readily palpable. Corpus luteum cyst may encourage torsion of the ovary, causing severe pain, or it may rupture and bleed, in which case laparotomy is usually required to control hemorrhage into the peritoneum. Unless these acute complications develop, symptomatic therapy is all that is required. The cyst will disappear within 2 months in nonpregnant women, and will gradually become smaller during the last trimester in pregnant women.

#### Theca Lutein Cysts.

Theca lutein cysts range in size from minute to 4 cm in diameter. They are usually bilateral, are filled with clear straw-colored and occasionally bloody serous fluid, and are found only in association with hydatidiform mole and chorioepithelioma. The cyst may rupture and bleed. The primary disease is suggested when an extremely high titer of chorionic gonadotropin is found in association with the cyst. The remote possibility of bilateral papillary cystadenoma should be considered in the differential diagnosis.

These cysts disappear spontaneously following elimination of the molar pregnancy or destruction of the chorioepithelioma.

#### Endometrial Ovarian Cysts.

Ectopic endometrium which implants on the ovary causes periodic (nonhormonally induced) bleeding. Attempts at "healing" follow each period, but invasion of the endometrial tissue eventually results in cyst formation. These cysts vary from microscopic in size up to 10-12 cm in diameter. They are filled with thick, chocolate-colored (old) blood, and are often adherent to neighboring viscera. The symptoms are infertility, hypermenorrhea, dyspareunia, and secondary or acquired dysmenorrhea. Not all "chocolate cysts" are of endometrial origin, since bleeding into any

cystic cavity will result in the accumulation of decomposed blood.

The treatment of large endometrial ovarian cysts is surgical removal, leaving as much functioning ovarian tissue as possible. Small cysts may be destroyed by electrocautery.

#### Fibromas of the Ovary.

About 5% of ovarian tumors are fibromas. They are unilateral, firm, nonfunctional, and benign, being composed principally of fibrous connective tissue. Fibromas are smooth, round, lobulated, and generally small, although a few have been reported which weighed as much as 2.25 Kg (5 lb). Fibromatous tumors are the principal cause of Meigs's syndrome. The abdomen enlarges and the patient complains of orthopnea, tachycardia, and chest oppression. Torsion often occurs, causing agonizing pain in the affected lower quadrant and nausea and vomiting. Larger tumors cause a sense of pelvic heaviness. The tumor is usually palpable on pelvic examination.

Meigs's syndrome must be distinguished from primary pulmonary and abdominal disease causing hydrothorax and ascites.

Treatment consists of surgical removal. Hydrothorax and ascites disappear immediately after removal of the tumor. Unless sarcoma is found on pathologic examination, the prognosis is excellent.

#### Brenner Tumor.

A Brenner tumor is a unilateral, firm, nonencapsulated, nonfunctioning neoplasm which consists of nests of epithelioid cells surrounded by whorls of dense connective tissue. It is often mistaken for fibroma. These tumors comprise 1% of all ovarian neoplasms. They are believed to arise from Walthard cell rests, but are occasionally found in the wall of a pseudomucinous cystadenoma. Brenner tumors may grow to 30 cm in diameter, although most are less than 2-3 cm. They are most common in women over 40 years of age, and are occasionally associated with Meigs's syndrome. They are nonmalignant.

Brenner tumors produce symptoms only by virtue of their size and situation, i.e., unilateral pelvic discomfort and a sense of fullness and heaviness in the lower abdomen. If torsion occurs it causes acute abdominal pain with nausea and vomiting.

Treatment consists of ovariectomy. If the tumor is in the wall of a cystadenoma, treatment is dictated by the clinical consequences of cystadenoma.

#### Teratoid Tumors.

Teratoid tumors may represent imperfect parthenogenesis. They are composed of one, two, or three germinal layers which may grow into any

possible combination of imperfectly formed structures. If one type of tissue predominates, the appearance will be that of a single-tissue tumor; such is the case in struma ovarii, the thyroid (iodine-containing) tumor of the ovary. Dermoid cysts, the most common type of teratoid tumor, contain ectodermal (and often mesodermal) tissue in the form of macerated skin, hair, bone, and teeth, the cyst is filled with a heavy, greasy sebaceous material and other structures. Teratoid tumors occur primarily in women 18-40 years of age. Dermoids account for 10% and solid teratomas 0-1% of all ovarian tumors. About 15% are bilateral.

The clinical manifestations of teratoid tumor are produced when the freely shifting mass distorts and displaces neighboring viscera. A teratoid is relatively light and rarely adherent. It tends to "float" upward in the abdomen, which encourages the development of a long pedicle, when torsion occurs, sudden, excruciating, persistent pain results. Rupture of a dermoid due to trauma or during pregnancy results in chemical peritonitis. If the neoplasm is large, the patient may complain of constipation and urinary frequency. Calcification may be observed on x-ray in the form of teeth or bone.

Teratoid tumor must be differentiated from pedunculated uterine myomas.

The treatment of teratoma is surgical removal and examination and aspiration of the other ovary to make certain that another dermoid is not present. Care should be taken not to spill the contents into the pelvic cavity, and teratomas should never be needed through the cul-de-sac for therapeutic or diagnostic reasons since leakage into the abdomen causes serious complications.

The prognosis is usually excellent. Malignant change, though uncommon, implies a poor prognosis.

#### Cystadenomas (Pseudomucinous & Serous Cystadenomas)

Cystadenomas are the most common of ovarian neoplasms, representing 70% of all ovarian tumors. These tumors produce no hormone and are most common in women between the ages of 45 and 65. The relative frequency of serous to pseudomucinous cystadenoma is about 1:1.

Pseudomucinous cystadenoma grows more sluggishly and becomes larger than the serous type, some have been reported to weigh over 4.5 Kg. (100 lb.). These tumors may be teratomas composed entirely of ectoderm. They are usually multilocular, contain a thick, viscid, brownish liquid, are lined by tall columnar epithelial and goblet cells; and are contained in a tough membranous capsule. About

5% are found to be malignant at surgery.

Serous cystadenomas do not become as large as pseudomucinous cystadenomas; most weigh 4.5-9 Kg. (10-20 lb.). They are unilocular, filled with a thin yellowish fluid, are lined by cuboidal or short columnar cells, and tend to develop papillary excrescences on both their inner and outer surfaces. Serous cystadenomas, like the pseudomucinous type, are also contained in a parchment-like capsule. Small sand-like, sharp, calcareous concretions (psammoma bodies) are often present within the tumor. Serous cystadenomas are felt to arise from invagination of the germinal epithelium of the surface of the ovary.

Cystadenomas are silent tumors because they do not produce hormones, pedicles form rarely, and the capsule does not rupture easily. Symptoms are produced only when the tumor becomes large enough to cause increased abdominal girth and weight gain, pelvic heaviness, constipation, and urinary frequency. The tumor is easily palpable on abdominal examination, and x-rays may show psammoma bodies. About 50% eventually become malignant.

Treatment consists of surgical removal of benign tumors by oophorocystectomy and panhysterectomy and bilateral salpingo-oophorectomy if malignant change has occurred. Radiation or intraperitoneal injection of chlorambucil or nitrogen mustard is indicated if peritoneal or visceral metastases are found.

All ovarian cysts over 7 cm. in diameter and those which persist for over 90 days should be removed.

#### Mesonephroma.

Mesonephroma is an uncommon nonfunctioning ovarian tumor which clinically and grossly resembles papillary serous cystadenoma. Most cases occur in patients over 35 and are probably of teratogenous origin. The tumor is often 10-20 cm. in diameter when first discovered. Thirty per cent are malignant. Salpingo-oophorectomy is necessary for cure. If it is likely that malignant change has occurred, panhysterectomy is required. Radiation therapy is of little value.

#### Arrhenoblastoma.

Arrhenoblastoma is a rare ovarian tumor (fewer than 175 cases have been reported) which occurs most frequently during the reproductive years and is assumed to arise from sexually ambivalent cells noted in the ovary of the 6-7 week embryo or to be of teratoid origin. The tumor is unilateral (more often on the right side), and may be minute or may fill the entire pelvis. Twenty-five per cent become malignant, but metastases are usually late.

Arrhenoblastomas are usually hormonally active, producing androgenic substances which cause both *defeminization and virilization*, manifested by varying degrees of amenorrhea, acne, hirsutism, recession of the hair-line at the forehead, slight alopecia, loss of feminine contour, breast and genital atrophy, clitoral hypertrophy and deepening of the voice. The urinary excretion of 17-ketosteroids is slightly to moderately increased, urinary dehydroepiandrosterone levels are strikingly high. The urinary hydroxysteroids are not elevated. The FSH titer is normal or minimally reduced.

Arrhenoblastoma must be distinguished from the adrenocortical disorders, a much more frequent cause of virilization which usually cause less virilization and a much more pronounced elevation of the urinary 17-ketosteroids.

Arrhenoblastoma should be removed surgically together with other pelvic reproductive organs unless the patient desires children and the tumor is clinically and histologically benign. In which case unilateral oophorectomy and salpingectomy are sufficient. Hormonal evaluation should be repeated after several months to determine recurrence.

### Virilizing Lipoid Cell Tumors

Virilizing lipoid cell tumors of the ovary are a group of rare small neoplasms occurring in women over 50 years of age and causing symptoms and signs of virilization such as hirsutism, masculine hair distribution, odor, perspiration, acne, and clitoral hypertrophy. Obesity is common. Hypertension, polycythemia, and diabetes mellitus have also been reported. The tumor is usually too small to be palpated. The excretion of 17-oxysteroids and 17-ketosteroids is elevated, and the urinary pregnanetriol level may be high.

These tumors must be differentiated from arrhenoblastoma and primary adrenal abnormalities. About 20% are malignant.

Treatment consists of surgical removal.

### Theca Cell Tumors\*

Theca cell tumors are rare functional feminizing ovarian neoplasms derived from ovarian stromal anlagen. They occur most frequently in young girls and postmenopausal women and vary in size from minute nodules to masses 30 cm in diameter. The ratio of incidence of theca cell tumors to granulosa cell tumors is 1:8, although pure theca cell tumors are rare. About 1% become malignant. The tumor is almost invariably unilateral.

Clinical and laboratory findings are identical with those of granulosa cell tumors. As is true of granulosa cell tumors also, theca cell tumor may rarely virilize rather than feminize.

As the cause of abnormal uterine bleeding, theca cell tumors must be differentiated from idiopathic precocious puberty, granulosa cell tumors, and uterine neoplasms.

Treatment for benign theca cell tumors is unilateral ovariectomy. Malignant tumors require total hysterectomy and bilateral salpingo-oophorectomy.

### Granulosa Cell Tumor\*

Granulosa cell tumors, the most common ovarian neoplasms of sex gland derivation, represent 3-4% of all ovarian tumors. They are solid tumors which vary in size from microscopic to 9 Kg (20 lb) and often produce estrogens. A rare tumor may be virilizing, however. Granulosa cell tumors are most often seen in women 50-70 years of age. Ten per cent are bilateral. Both granulosa and theca cells are always found together in these tumors. About 15-20% are malignant but metastasis is almost always confined to neighboring genital organs.

The clinical manifestations of granulosa cell tumors are secondary to the production of large amounts of estrogen. In children this causes early development of pubic hair, hypertrophy of the breasts, and enlargement of the labia cervix and uterus. Advanced bone age and early epiphyseal closure (dwarfism) will occur if hormonal stimulation is continued for a long period. In the functional years, menometrorrhagia is usually the only finding. In postmenopausal women, re-feminization and re-institution of uterine bleeding occur. Very large tumors may cause symptoms secondary to abdominal distention, displacement of the pelvic structures, or torsion of the pedicle. Ascites often occurs when the neoplasm is malignant. On pelvic examination a mobile, rarely adherent, often soft and cystic mass is palpable in the adnexa. Laboratory findings consist of elevated urinary estrogens and a high degree of cornification as demonstrated in the vaginal smear.

Granulosa cell tumors must be differentiated from other causes of postmenopausal bleeding or abnormal menstruation, and other functional tumors (e.g., lipoid cell tumors and theca cell tumors of the ovary).

\*Pure granulosa cell tumors of the ovary are rare, theca cells are almost always present also. It would be more appropriate to speak of granulosa-theca cell tumors or theca-

granulosa cell tumors, depending upon which type of cell predominates. The 2 types are dealt with separately here in order to simplify discussion.

Treatment consists of surgical removal in patients in the functional or prepubertal years, benign tumors are removed by ovariectomy in postmenopausal women, total hysterectomy and bilateral salpingo-oophorectomy is indicated

### Dysgerminoma,

Dysgerminoma is a nonfunctioning, potentially malignant ovarian tumor (About 4% of all primary malignant ovarian tumors are dysgerminomas and about a third of dysgerminomas are cancerous) Dysgerminoma is bilateral in one-third of cases, and is most common in women 10-30 years of age. It is thought to be of teratoid origin. Although usually small when found (4-7 cm in diameter) dysgerminomas may grow rapidly to fill the entire pelvis. The tumor is often discovered in patients with underdeveloped secondary sex characteristics such as occur in female pseudohermaphrodites. The same tumor found in a male is called a seminoma.

Symptoms are usually due to abdominal enlargement caused by rapid tumor growth and ascites. Severe abdominal distress and acute pain may result if the thin capsule ruptures. Weekly false-positive pregnancy tests have been reported in some cases.

Other nonfunctioning ovarian tumors (e.g. a teratoma, cystadenoma) must be considered in the differential diagnosis.

Treatment usually consists of surgical removal of the tumor and all pelvic reproductive organs, but if the tumor is small, unilateral and histologically benign and if the patient desires to maintain reproductive function, oophorectomy may be feasible.

Underdeveloped secondary sex characteristics do not improve after removal of the tumor.

### Secondary Ovarian Cancer

In 10% of cases of fatal malignant disease in women the ovary is found to be secondarily involved by metastasis or extension of malignancy, usually from the uterus or the ovary (although one-third represent metastasis from stomach cancer). The intestine, breast, thyroid, kidney, and adrenals may also be primary foci. One of the most important carcinomas which metastasizes to the ovaries is the Krukenberg tumor, which usually originates in the stomach, involves both ovaries and presents as a large mucin-producing, buff-colored, solid lobulated, often kidney-shaped, nonadherent tumor with a heavy capsule. The importance of these secondary ovarian cancers is that they must be distinguished from primary ovarian tumors.

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## PSYCHOGENIC PELVIC PAIN

Functional pelvic pain is variously reported to occur in 5-25% of gynecologic patients. The diagnosis is established by ruling out organic causes and wherever possible by eliciting a consonant family history. A fairly characteristic "profile" of the typical woman with psychogenic pain is as follows: she is egotistical and vain, demanding and self-indulgent, shallow, dramatic, emotionally labile and inconsistent, and coquettish but relatively frigid.

### Differential Diagnosis of Organic & Psychogenic Pain

	Organic Pain	Psychogenic Pain
Type	Sharp cramping intermittent	Dull continuous
Time of onset	Any time May awaken patient	Usually begins well after waking when social obligations are pressing
Radiation	Follows definite neural pathways	Bizarre pattern or does not radiate
Localization	Localizes with typical point tenderness	Variable, shifting generalized
Progress	Soon becomes either better or worse	Remains the same for weeks, months, years
Provocative tests	Often reproduced or augmented by tests or manipulation not by mood	Not triggered or accentuated by examination but by interpersonal relationships

### Treatment.

Any woman who complains of pelvic pain must have a thorough diagnostic evaluation, in a hospital if necessary. Reassurance and symptomatic therapy are always indicated, and may be all that the physician can provide. Since the basic disorder is a psychic one, the physician must be prepared to spend a great deal of time with these women. Do not give narcotics and do not operate except upon definite surgical indications. Be wary of prescribing sedatives as these patients are poor suicidal risks.

### Prognosis

Since these women often refuse therapy withdraw from a treatment program soon after it is well under way, and change physicians frequently, their medical future is bleak. In general, they are unwilling to abandon invalidism as a way of life.

Of those patients who can be persuaded to submit to psychiatric care over half will show marked improvement and many will be cured. Reassurance and symptomatic therapy give temporary improvement in about three-fourths of cases.

## GYNECOLOGIC BACKACHE

Gynecologic backache is usually due to a well-defined pelvic disorder. It is most often seen during the childbearing years and is more common among women who have had several children. Multiple causes are the rule (gynecologic combined with orthopedic, urologic, or neurologic disease). Gynecologic causes include the following: (1) Traction or pulsion on the peritoneum, the supportive structures of the generative organs, or the pelvic floor (tumors, ascites, uterine prolapse); (2) Inflammation of the pelvic contents: bacterial infection (peritonitis, salpingitis) or chemical irritation (due to iodine used in salpingography, fluid from a ruptured dermoid cyst); (3) invasion of pelvic tissues or bone by tumor or endometriosis; (4) Obstruction of the genital tract (cervical stenosis); (5) Torsion or constriction of pelvic viscera (ovary enmeshed in adhesions, twisted ovarian cyst); (6) Congestion of internal genitalia (turgescence of the retroposed uterus, backache during menstruation); (7) Psychologic tension (anxiety, apprehension).

### Clinical Findings

**A Symptoms and Signs.** Constant lumbosacral or sacral backache is often due to sal-

pingitis, pelvic abscess, or a twisted ovarian cyst. Back pain due to endometriosis of the cul-de-sac is referred to the coccygeal region or rectum. Ovarian, renal, and ureteral backache commonly radiates down the back into the buttocks or along the distribution of the sciatic nerves.

The major symptoms and signs of the underlying pelvic disease are almost always present.

**B Laboratory Findings.** Infection will be reflected in the routine blood studies. Cytologic study of vaginal exudate may reveal neoplastic cells or bacteria.

**C X-ray Findings.** Anteroposterior and lateral films of the spine often disclose a postural degenerative neoplastic, or orthopedic cause of backache. Myelograms may be required to demonstrate a herniated intervertebral disk.

### Treatment

Successful treatment of the underlying disease is the only curative procedure. Supportive measures include the following: (1) Bed rest on a firm mattress, permitting the patient to seek the most comfortable position; (2) Local heat; (3) Warm water douches; (4) Aspirin or aspirin with codeine; (5) Ataraxics, e.g., prochlorperazine (Compazine®) 5-15 mg t.i.d., to reduce emotional tension.

### Prognosis

Gynecologic backache almost always subsides with treatment of the underlying pelvic disorder.

## INFERTILITY

A couple is said to be infertile (1) if pregnancy does not result after one year of normal marital relations without contraceptives, (2) if the woman conceives but aborts repeatedly, or (3) if the woman bears one child but aborts repeatedly or fails to conceive thereafter. About 10% of marriages are infertile. Female infertility may be due to nutritional deficiencies, hormonal imbalance, developmental anomalies of the reproductive organs, infections or tumors. Male infertility is usually due to sperm deficiencies (low sperm count, morphologic abnormalities) or impaired motility. About 40% of cases of infertility are the responsibility of the male partner.

## OBSTETRICS

Treatment depends upon accurate diagnosis of the many systemic or local factors which may be involved. Pregnancy often follows correction of metabolic disorders, anemia, or infection corticosteroids for Cushing's disease or Stein-Leventhal syndrome, or androgen (rebound) therapy of the male partner. Surgical correction of anatomic abnormalities in the female is often possible. There is no treatment for male azoospermia.

The prognosis for conception and normal delivery is good if minor (even multiple) disorders can be identified and treated early, poor if the causes of infertility are severe, untreatable, or of prolonged duration. If treatment is not successful within one year, the physician must consider whether he should recommend adoption.

Suggested Four-visit Routine for Evaluation of Infertility

	Wife	Husband
First visit	Joint discussion of problem of infertility	
	Medical history	Medical history
	Explanation	Explanation
	Taking and recording of BBT	Semen collection and analysis
Second visit (2-4 weeks later) at mid-cycle	Physical examination Routine and indicated laboratory tests Preliminary evaluation of BBT chart	Physical examination Routine and indicated laboratory tests Semen analysis discussed
Third visit (4 weeks later)	Tubal insufflation (Rubin's test) Evaluation of BBT chart	Repeat semen analysis if first was deficient
Fourth visit (4 weeks later)	Spinnbarkelt and fern test Sims-Huhner test Repeat Rubin's test if first was unsuccessful	
Later tests (as indicated)	Hysterosalpingography when 2 Rubin tests indicate occlusion Vaginal smear series Endometrial biopsy Culdoscopy Laparotomy.	Testicular biopsy, when indicated Cystoscopy Definitive genitourinary surgery

### DIAGNOSIS & DIFFERENTIAL DIAGNOSIS OF PREGNANCY

In about one-third of cases it is difficult to make a definitive diagnosis of pregnancy before the second missed period because of the variability of the physical changes induced by pregnancy, the possibility of tumors, and because obesity and poor patient relaxation often interfere with the examination. Even experienced physicians sometimes make "false-positive" and "false-negative" diagnoses of pregnancy. The potentially grave emotional and legal consequences of an incorrect diagnosis of pregnancy should make the physician cautious, if he is in any doubt, he should schedule a reexamination in 3-4 weeks. If the patient demands earlier confirmation, a pregnancy test can be ordered (see p. 398).

#### Manifestations of Pregnancy.

**A Presumptive Manifestations** The following symptoms and signs are usually due to pregnancy but even 2 or more are not diagnostic. A record or history of time and frequency of coitus may be of considerable value.

**1 Symptoms** - Amenorrhea, nausea and vomiting (first trimester), breast tenderness and tingling (after 1-2 weeks), urinary frequency and urgency (first trimester), "quickening" (may appear at about the 16th week), weight gain.

**2 Signs** - Skin pigmentation (after 16th week), epulis (after first trimester), breast changes (enlargement, vascular engorgement, colostrum), abdominal enlargement, cyanosis of vagina and cervical portio (about the sixth week), softening of the cervix (fourth or fifth week), softening of the cervicouterine junction (fifth or sixth week), irregular softening and slight enlargement of the fundus (about the fifth week), generalized enlargement and diffuse softening of the corpus (after eighth week).

**B Probable Manifestations (After 28th Week)** Uterine enlargement, uterine souffle (bruit), uterine contractions.

**C. Positive Manifestations** Any of the following, none of which is usually present until the fourth month, is undeniable medical and legal proof of pregnancy: auscultation of the fetal heart, palpation of the fetal outline, recognition of fetal movements by the physician, demonstration of fetal skeleton by x-ray.

## Laboratory Pregnancy Tests

Name	Test Animal*	Procedure	Time, Accuracy	Pregnancy Indicated By	Remarks
Aschheim Zondek	5 mice (3 weeks old)	0.4 ml patient's first morning urine (acidified), injected 6 X during 2 days	96 hrs (98%)	Ovulation (corpus luteum)	Moderately expensive. Need mouse colony, multiple injections
Friedman-Hoffman	Rabbit (10-12 weeks old)	2.5 ml patient's serum injected into rabbit's ear vein	24 hrs (96%)	Ovulation (corpus luteum)	Moderate cost. Relatively simple test
Hogben	So African clawed toad ( <i>Xenopus laevis</i> )	80 ml concentrated protein precipitated extracted 1 ml injected into dorsal lymph sac of toad (or serum 0.5 ml injected q 4 hrs X 3)	18 hrs (98%)	Ovulation (eggs in bottom of tank)	Moderate cost, simple. False-positives rare
Grall-Mainini	2 frogs or toads ( <i>Rana pipiens</i> or <i>Bufo arenarum</i> )	1 ml patient's first morning urine injected into dorsal lymph sac of each of 2 male frogs or toads	1.3 hrs (98%)	Sperm in urine from cloaca	Low cost. Simple, rapid. False-positives rare

\*If the animal dies the test should be repeated. Be certain the patient is not taking any medication.

## Clinical Pregnancy Tests

Name	Procedure	Accuracy	Interpretation and Remarks
Basal body temperature (BBT)	Daily oral temperatures with special thermometer under basal conditions (immediately upon awakening each day before getting out of bed or smoking). Readings are plotted on a chart provided for the purpose.	98%	Daily temperature recording must be begun before ovulation. The normal ovulatory cycle will show a flat temperature curve before ovulation. On the day of ovulation a sharp rise (as much as 1°) occurs. Persistence of this rise for more than 14 days is a probable manifestation of pregnancy. A flat curve during the entire cycle, i.e., absence of the mid cycle rise, indicates failure of ovulation. Other rises may be due to patient error, failure to observe basal conditions, or illness.
Neostigmine	Neostigmine (Prostigmin®) methylsulfate 1 ml (1:1000) I.M. for 3 successive days	90%	If uterine bleeding does not occur after the first or second injection or within 72 hours after the third injection, and if other causes of secondary amenorrhea have been ruled out, pregnancy is probable since an intact corpus luteum is required for bleeding. Although the test is easy, inexpensive, and fairly rapid, the fact that it is a "negative type" test impairs its value.
Estrogen-progesterone	Progesterone 20 mg and estradiol benzoate 2 mg i.M.	90%	If bleeding does not occur within 10 days after administration of estrogen-progesterone or 7 days after administration of progesterone, norethindrone, or norethynodrel, and if other causes of amenorrhea have been ruled out, pregnancy is probable. Note: If bleeding occurs, the test is inconclusive.
Progesterone	Delalutin® 250 mg (2 ml) i.M.	95%	
Norethindrone	Norethindrone (Norlutin®) 20 mg orally	95%	
Norethynodrel	Norethynodrel (Enovid®), 20 mg orally	95%	



**Differential Diagnosis of Pregnancy.**

All of the presumptive and probable symptoms and signs of pregnancy can be caused by other conditions, and all the clinical and laboratory tests indicative of pregnancy may be positive in the absence of conception. Clinical experience and often the passage of time with reexamination are required to establish the correct diagnosis. The most common disorders which may be confused with pregnancy are uterine and adnexal tumors.

### MINOR DISCOMFORTS OF NORMAL PREGNANCY\*

**Backache.**

Virtually all pregnant women suffer from at least minor degrees of lumbar backache during gestation. Postural and other back strain, especially during the last trimester and relaxation of the pelvic joints due to the steroid sex hormones and perhaps relaxin are also responsible for backache.

The following measures are valuable both as prevention and treatment.

**A. Improved posture.** Stress the "tall" posture, with abdomen flattened as much as possible, the pelvis tilted forward and the buttocks "tucked under" to straighten the back.

**B. Exercise to "tone" and maintain muscle strength.**

**C. Heels for general wear** should be of medium height to further straighten the back, particularly when flat footwear has been worn extensively.

**D. A firm mattress.** Avoid sag which may cause painful, prolonged flexion of the back (after exaggerated extension while erect). Bed-boards between the springs and mattress often provide welcome support.

**E. Local heat and light massage** to relax tense, taut back muscles.

**F. A maternity girdle** may be indicated for patients with backache due to extreme lordosis or kyphoscoliosis or associated with obesity or multiple pregnancy.

**G. Analgesics** will be adequate for mild distress. Carisoprodol (Rela<sup>®</sup>, Soma<sup>®</sup>), 350 mg. orally q i.d. (or a comparable seda-

tive or muscle relaxant drug) gives temporary relief.

**H. Orthopedic evaluation** is necessary when disability results from backache. Note neurologic signs and symptoms indicative of intervertebral disk syndrome or other nerve compression problems, radiculitis.

**Syncope & Faintness.**

**Syncope and faintness** are most common in early pregnancy. Vasomotor instability, often associated with postural hypotension, results in transient cerebral hypoxia and pooling of blood in the legs and in the splanchnic and pelvic areas, especially after prolonged sitting or standing in a warm room. Hypoglycemia before or between meals, more common during pregnancy, may result in "lightheadedness" or even fainting.

These attacks can be prevented by avoiding inactivity and utilizing deep breathing, vigorous leg motions, and slow change of motion. Encourage the patient to take 6 small meals a day rather than 3 large ones. Stimulants (spirits of ammonia, coffee, tea, or amphetamines) are indicated for attacks due to hypotension. Food for hypoglycemia.

**Urinary Symptoms.**

Urinary frequency, urgency, and stress incontinence are quite common, especially in advanced pregnancy. They are due to reduced bladder capacity and the pressure of the presenting part upon the bladder.

Suspect urinary tract disease, especially infection, if dysuria or hematuria is reported.

When urgency is particularly troublesome, the patient should avoid coffee, spices, and alcoholic beverages. The following bladder sedative mixture is often useful.

$\mathcal{R}$ Tincture hyoscyamus	30.0 (1 oz.)
Potassium citrate	50.0 (1 2/3 oz.)
Water, q a ad	120.0 (4 oz.)

Sig. One tsp. in water orally every 4 hours p r n

**Heartburn.**

Heartburn (pyrosis or "acid indigestion") results from gastroesophageal regurgitation. In late pregnancy, this may be aggravated by displacement of the stomach and duodenum by the uterine fundus.

About 15% of all pregnant patients experience severe pyrosis (as well as nausea and vomiting) during the latter portion of pregnancy because of diaphragmatic hiatus hernia. This develops with "tenting" of the diaphragm and flaring of the lower ribs after the seventh or eighth month of pregnancy. The hernia is

\*Morning sickness is discussed with Vomiting of Pregnancy on p. 400.

reduced spontaneously by parturition. Symptomatic relief, not surgery, is recommended

**A. Neostigmine bromide (Prostigmin®).** 15 mg. (1/4 gr.) orally t i. d. as necessary to stimulate gastrointestinal secretion and motility.

**B. Acidifying Agents** Glutamic acid hydrochloride, 0.3 Gm. t i. d., before meals (Hydrochloric acid solutions damage the teeth) Avoid antacids during early pregnancy because gastric acidity is already low at this time

**C. Hard candy, hot tea, and change of posture** are helpful In late pregnancy, antacids containing aluminum hydroxide gel to reduce gastric irritation are beneficial

#### Constipation.

Bowel sluggishness is common in pregnancy. It is due to suppression of smooth muscle motility by increased steroid sex hormones, and pressure upon and displacement of the intestines by the enlarging uterus Constipation frequently causes hemorrhoids and aggravates diverticulosis and diverticulitis

**A. General Measures** Stress good bowel habits The patient should try for a bowel evacuation at the same time every day The diet should consist of bulk foods, including roughage (unless contraindicated by gastrointestinal intolerance), laxative foods (citrus fruits, apples, prunes, dates, and figs), and a liberal fluid intake Encourage exercise (walking, swimming, calisthenics)

#### B. Medical Treatment.

1. To soften the stool, give bulk laxatives and "smoothe" agents which are neither absorbed by nor irritating to the bowel By accumulating fluid volume, they increase peristalsis. Dioctyl sodium sulfosuccinate (Colace®, Dioxinate®) is detergent Psyllium hydrophilic mucilloid (Metamucil®) is hydrophilic

2. Prescribe mild laxatives in more severe cases. These include cascara and phenolphthalein Milk of magnesia and Epsom salts are also useful in small doses

3. Avoid purges for fear of inducing labor Do not prescribe mineral oil since it prevents absorption of fat-soluble vitamins when administered in large amounts

#### Hemorrhoids.

Straining at stool and bearing down at delivery often cause hemorrhoids, especially in women prone to varicosities. For these reasons it is best to prevent or treat constipation early and to deliver by elective low forceps, with episiotomy when desirable

**A. Medical Measures:** Gently replace the hemorrhoid, if this can be done easily. Warm (or cool) sitz baths or compresses are helpful Anesthetic ointments such as dibucaine (Nupercaine®) and cyclomethycaine (Surfacaine®) can be used for relief of pain If used sparingly, the following ointment is safe and most effective in relieving rectal pain

<b>R</b>	<b>Cocaine hydro-</b>	
	<b>chloride</b>	0.3 (5 gr.)
	<b>Phenol</b>	0.6 (10 gr.)
	<b>Petrolatum</b>	
	<b>Lanolin aa</b>	15.0 (4 dr.)

**Sig** Apply a small amount to the anus 1-4 times daily p r n

Insert an Anusol® or another astringent, anesthetic, emollient cone rectally b i. d. or at bedtime to aid bowel evacuation

**B Surgical Treatment** Incise recently thrombosed, painful hemorrhoids under local anesthesia and evacuate the clot Do not suture Order sitz baths, rectal ointments, suppositories, and mild laxatives postoperatively

Injection treatments to obliterate hemorrhoids during pregnancy are contraindicated They may cause infection and extensive thrombosis of the pelvic veins, and are rarely successful because of the great dilatation of many vessels

#### Breast Soreness.

Physiologic breast engorgement may cause discomfort, especially during early and late pregnancy A well-fitting brassiere worn 24 hours a day affords relief Ice caps are temporarily effective. Hormone therapy is of no value

#### Headache.

Headache is most disturbing during the first and third trimesters. Emotional tension is the most common cause, consider anxiety, uncertainty, and similar psychic causes when headache is migrainous, band-type, occipital, or more or less constant Refractive errors and ocular imbalance are not caused by normal pregnancy, but the pregnant woman tends to be sedentary and may read or sew more despite "eyestrain" Hormonal stimulation causes vascular engorgement of the nasal turbinates, and the resultant congestion and epistaxis contribute to sinusitis and headache.

Severe, persistent headache in the last trimester must be regarded first as symptomatic of toxemia of pregnancy.

The belief that pituitary swelling during normal pregnancy causes headache is without foundation

Discuss the patient's difficulties in an attempt to relieve her fears and resolve minor conflicts. "Work through" the major problem to a solution to relieve chronic, psychogenic headache.

Obtain ophthalmologic studies, which may reveal the need for corrective lenses or eye exercises. Insist on adequate illumination for reading and close work.

Nasopharyngeal examination may disclose abnormalities. Give phenylephrine (Neo-Synephrine®) nose drops, 0.25%, for catarrh and epistaxis. Oily solutions are preferred these soften crusts and prevent mucosal drying which predisposes to nosebleed.

Analgesics may be given as necessary for temporary relief. Ataractics may calm the "nervous" woman.

### Ankle Swelling

Edema of the lower extremities not associated with toxemia develops in two-thirds of women in late pregnancy. Edema is due to sodium and water retention as a result of ovarian, placental, and adrenal steroid hormones, normally increased venous pressure in the legs, varicose veins with venous congestion, prolonged sitting or standing, and elastic garters.

Treatment is largely preventive and symptomatic, since nothing can be done about the activity of the pregnancy hormones. The patient should elevate her legs frequently and sleep in a slight Trendelenburg position. Circular garters and clothing which interfere with venous return should not be worn.

Restrict salt intake and provide elastic support for varicose veins (see below).

### Varicose Veins.

Varicosities are usually a problem of the multipara, and may cause severe complications. They are due to weakness of the vascular walls, increased venous stasis in the legs due to the hemodynamics of pregnancy, inactivity and poor muscle tone, and obesity, since the excessive tissue mass requires increased circulation and fatty infiltration of connective tissue impairs vascular support.

Serious phlebothrombosis and thrombophlebitis often complicate the puerperium, but they are uncommon during pregnancy. Pulmonary emboli are infrequent but are often septic.

The vulvar, vaginal, and even the inguinal veins may be markedly enlarged during pregnancy. Damaged vulvovaginal vessels give rise to hemorrhage at delivery.

Large vulvar varices cause pudendal discomfort. A vulvar pad wrapped in plastic film, snugly held by a menstrual pad belt or T-binder, gives relief.

Anticoagulants may be required in acute thrombophlebitis. Heparin is preferred to bishydroxycoumarin since it does not cause fetal damage, is more easily controlled, and is not excreted in the milk. However, neither drug, whether administered before or during labor, causes increased bleeding from the uterus, sufficient mechanical compression of the myometrial vessels prevents excessive blood loss despite increased blood coagulation time. Cervical, vaginal, and perineal lacerations may bleed more briskly if the patient has received heparin or bishydroxycoumarin.

Injection treatment of varicose veins during pregnancy is futile and hazardous.

In all other respects management is the same as in nonpregnant women (see Chapter 9).

### Leg Cramps.

Cramping or "knotting" of the muscles of the calves, thighs, or buttocks may occur suddenly after sleep or recumbency after the first trimester of pregnancy. For unknown reasons it is less common during the month prior to term. Sudden shortening of the leg muscles by "stretching" with the toes pointed precipitate the cramp. It is believed that cramps are due to reduction in the level of diffusible serum calcium or increase in the serum phosphorus level (or both). This follows excessive dietary intake of phosphorus in milk, cheese, meat, or dicalcium phosphate, diminished calcium intake, or impaired calcium absorption. Fatigue and sluggish circulation in the extremities are contributory factors.

**A Immediate Treatment.** Requires the patient to stand barefooted on a cold surface (e.g., a tiled bathroom floor). Rub and "knead" the contracted painful muscles. Passively flex the foot to lengthen the calf muscles. Apply local heat.

### B Preventive and Definitive Treatment

1 Reduce dietary phosphorus intake temporarily by limiting meat to one serving daily and milk to one pint daily. Discontinue dicalcium phosphate and other medications containing large amounts of phosphorus.

2 Eliminate excess phosphorus by absorption with aluminum hydroxide gel, 0.5-1 Gm (7½-15 gr.) orally in liquid or tablet form with each meal.

3 Increase the calcium intake by giving calcium lactate, 0.5 Gm. (10 gr.) (or equivalent) orally t.i.d. before meals. Even larger doses may be required if the absorption of calcium from the intestinal tract is impaired.

4 Avoid walking with the toes pointed forward ("Lead with the heel").

**Abdominal Pain.**

Intra-abdominal alterations causing pain during pregnancy include the following

**A Pressure** Pelvic heaviness, a sense of "sagging" or "dragging," relate to the weight of the uterus on the pelvic supports and the abdominal wall. Frequent rest periods in the supine or lateral recumbent position and a maternity girdle are recommended.

**B Round Ligament Tension Tenderness** along the course of the round ligament (usually the left) during late pregnancy is due to traction on this structure by the uterus with rotation of the uterus and change of the patient's position. Local heat and treatment as for pressure pain are effective.

**C Flatulence, Distention, and Bowel Cramping** Large meals, fatty gas-forming foods, and chilled beverages are poorly tolerated by pregnant women. Mechanical displacement and compression of the bowel by the enlarged uterus, hypotonia of the intestines, and constipation predispose to gastrointestinal distress. Correct, simplify and reduce food intake at any 1 meal. Maintain regular bowel function and prescribe mild laxatives when indicated. Exercise and change position frequently.

**D. Uterine Contractions** Braxton-Hicks contractions of the uterus are a normal phenomenon which may be startling to hyperreactive women. The onset of premature labor must always be considered when forceful contractions develop, but if contractions remain infrequent and brief the danger of early delivery is not significant. Analgesics and sedatives may be of value. Codeine is rarely required.

**E Intra-abdominal Disorders** Pain due to obstruction or inflammation involving the gastrointestinal, urinary, nervous, or vascular system must be diagnosed and treated specifically.

**F. Uterine or Adnexal Disease** Consider and treat pathologic pregnancy and tubal or ovarian disease appropriately.

**VOMITING OF PREGNANCY**

(Morning Sickness) &amp;

**HYPEREMESIS GRAVIDARUM**

(Pernicious Vomiting of Pregnancy)

About three-fourths of women, most of them primiparas, complain of nausea and vomit-

ing during pregnancy ("morning sickness"). About one woman in 200 develops hyperemesis gravidarum and requires hospitalization. Hyperemesis gravidarum can be fatal if it is not controlled.

The etiology of vomiting during pregnancy is not known, although various physiologic mechanisms have been postulated to account for it. Psychogenic factors are prominent in most cases.

**Clinical Findings**

**A Symptoms and Signs** The onset is most commonly during the fifth or sixth week of pregnancy, and the disorder usually persists only until the 14th to 16th week. Symptoms are most severe in the morning upon arising. Nutritional deficiencies are almost never noted. Hyperemesis gravidarum which continues unchecked is characterized clinically by dehydration, weight loss, avitaminosis, and jaundice.

**B Laboratory Findings** Severe vomiting causes hemoconcentration, decreased serum proteins and alkali reserves, and elevation of BUN, serum sodium chloride, and serum potassium. Ketone bodies are present in the concentrated urine specimen. Slight proteinuria is a common finding.

**C Ophthalmoscopic Examination** Retinal hemorrhages and retinal detachment are unfavorable prognostic signs.

**Differential Diagnosis**

Vomiting during pregnancy may be due to any of the diseases with which vomiting is usually associated, e.g., infections, poisoning, neoplastic diseases, hyperthyroidism, gastric disorders, gallbladder disease, intestinal obstruction, diabetic acidosis, uremia due to any cause, and hydatidiform mole.

**Complications**

The most serious complication of hyperemesis gravidarum is jaundice due to so-called "toxic hepatitis." Intraocular hemorrhage and retinal detachment may cause permanent blindness.

**Treatment.**

**A. Mild Nausea and Vomiting of Pregnancy** Reassurance and dietary restrictions are all that is required in many instances. In general, dry foods at frequent intervals are indicated. Restrict fatty, odorous foods, spiced dishes, and items which do not appeal to the patient.

Sedatives and antiemetics may be required. Vitamins are of no value unless deficiencies have developed. Antihistamines are useful for their sedative effect. Amphet-

amines may be given for their mood-elevating effect. Narcotics have no place in the treatment of digestive disorders of pregnancy.

**Note:** The possibility of teratogenicity of many drugs, including some antileptics, cannot be overlooked in selecting patients for medical treatment of nausea of pregnancy and in deciding which drugs to use and in what dosages. In general, it is probably best to give medical treatment only when urgently required, to avoid new and experimental drugs and all drugs which have been suggested as potential teratogens; and to give the lowest dosage which is consistent with clinical efficacy.

When symptomatic drug therapy is required, give phenobarbital, 30-60 mg ( $\frac{1}{2}$ -1 gr.), perphenazine (Trilafon®), 8 mg orally or rectally on arising and again at bedtime, or promethazine (Phenergan®), 50 mg orally or rectally 2 or 3 times daily. A useful sedative-antispasmodic mixture is as follows

R Tr. belladonna 30.0 (1 oz.)  
Elixir phenobarbital 240.0 (8 oz.)

Sig. One tsp. every 4 hours, or  
one hour before meals.

**B. Hyperemesis Gravidarum:** Hospitalize the patient in a private room at complete bed rest without bathroom privileges. Allow no visitors (not even the husband) until vomiting ceases and the patient is eating. Give nothing by mouth for 48 hours, and order appropriate parenteral fluids with vitamin and protein supplements as indicated. If there is no response after 48 hours, institute nasogastric tube feeding of a well-balanced liquid baby formula by slow drip. As soon as possible, place the patient on a dry diet consisting of 6 small feedings daily with clear liquids one hour after eating.

If the clinical situation continues to deteriorate in spite of therapy, therapeutic abortion may be required. The indications are delirium, blindness, tachycardia at rest, jaundice, anuria, and hemorrhage.

#### Prognosis.

Vomiting of pregnancy is self-limited, and the prognosis is good. Intractable hyperemesis gravidarum is a real threat to the life of the mother and the fetus.

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## ECTOPIC PREGNANCY

### Essentials of Diagnosis.

- Abnormal menstrual bleeding with symptoms suggestive of pregnancy.
- Cramping pains in the lower abdomen.
- Decidual tissues passed with blood (frequently).
- A tender mass palpable outside the uterus.

The presence of clinical and laboratory findings suggestive or diagnostic of pregnancy will distinguish ectopic pregnancy from many acute abdominal illnesses, such as acute appendicitis, a ruptured corpus luteum cyst or ovarian follicle, a twisted ovarian cyst, and urinary calculi. Uterine enlargement with clinical findings similar to those found in ectopic pregnancy is characteristic of an aborting uterine pregnancy or hydatidiform mole.

### General Considerations.

Any pregnancy arising from implantation of the ovum outside the cavity of the uterus is ectopic. Ectopic implantation occurs in about one out of 200 pregnancies. About 98% are tubal. Other sites of ectopic implantation are the abdomen, the ovary, and the cervix. Combined extrauterine and intrauterine pregnancy may occur. Only tubal ectopic pregnancy will be discussed in the following paragraphs.

### Clinical Findings.

**A. Symptoms and Signs.** The cardinal symptoms and signs of tubal pregnancy are (1) amenorrhea or a disordered menstrual pattern, followed by (2) uterine bleeding, (3) pelvic pain, and (4) pelvic (adnexal) mass-formation. It may be acute or chronic.

1. Acute (about 40% of tubal ectopic pregnancies) - Severe lower quadrant pain occurs in almost every case. It is sudden in onset, lancinating, intermittent, and does not radiate. Backache is present during attacks. Abnormal uterine bleeding is present in 80% and a pelvic mass is palpable in 70%. Collapse and shock occur in about 10%, often after pelvic examination. Two-thirds of patients give a history of abnormal menstruation. Most are infertile.

2. Chronic (about 40% of tubal ectopic pregnancies) - Blood leaks from the tube over a period of days, and considerable blood may accumulate in the peritoneum. Slight but persistent vaginal spotting is reported, and a

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2. Chronic (about 40% of tubal ectopic pregnancies) - Blood leaks from the tube over a period of days, and considerable blood may accumulate in the peritoneum. Slight but persistent vaginal spotting is reported, and a

bed rest with side rails for protection during convulsions. Allow no visitors. Do not disturb the patient for unnecessary procedures (e.g. baths, enemas, douches) and leave the BP cuff on her arm. Turn her on her side to prevent the caval syndrome and aspiration of vomitus. A padded tongue-blade should be kept at hand to be placed between her teeth during convulsions. A bulb syringe and catheter or suction machine to aspirate mucus or vomitus from the glottis or trachea, oxygen and an oxygen cone or tent (since masks and nasal catheters produce excessive stimulation). Typed and cross-matched whole blood must be available for immediate use because patients in eclampsia often develop premature separation of the placenta with hemorrhage and are susceptible to shock.

2 Laboratory evaluation - Insert a retention catheter for accurate measurement of the quantity of urine passed. Determine the protein content of each 24-hour specimen until the fourth or fifth postpartum day. NPN,  $\text{CO}_2$ , combining power and content and serum protein should be determined as often as the severity and progression of the disease indicate. If serum protein is below 5 Gm/100 ml, give 250-500 ml of serum albumin. If salt-poor serum albumin is not available, give plasma or serum.

3 Physical examination - Check BP hourly during the acute phase and every 2-4 hours thereafter. Observe fetal heart tones every time the BP is obtained. Perform ophthalmoscopic examination once a day. Examine the face, extremities and especially the sacrum (which becomes dependent when the patient is in bed) for signs of edema.

4 Diet and fluids - If the patient is convulsing, give nothing by mouth. Record fluid intake and output for each 24-hour period. If she can eat and drink, give a salt-poor (less than 1 Gm salt per day) high-carbohydrate, high-protein, low-fat diet (1500 Cal). Provide potassium chloride as a salt substitute. If the urine output exceeds 700 ml/day, replace the output plus visible fluid loss with salt-free fluid (including parenteral fluid) each day. If the output is less than 700 ml/day, allow no more than 2000 ml of fluid per day (including parenteral fluid). Give 200-300 ml of a 20% solution of dextrose in water 2-3 times a day during the acute phase to protect the liver, to replace fluids and to aid nutrition. (Do not give 50% glucose. It will sclerose the veins.) Use no sodium-containing fluids (e.g. Ringer's injection). Give 25-50 ml salt-poor albumin or 250-500 ml of plasma or serum if the patient is oliguric or if the serum protein is low.

5 Sedatives - Give a sedative upon admission to the hospital and maintain mild sedation until improvement is established.

6 Delivery - Because severe hypertensive disease, renal disease and toxemia of pregnancy are usually aggravated by continuing pregnancy, the most direct method of treatment of any of these disorders is termination of pregnancy. Control eclampsia before attempting induction of labor or delivery. Induce labor preferably by amniotomy alone when the patient's condition permits. Use oxytocin (Pitocin®) to stimulate labor if necessary. Regional anesthesia (preferably pudendal block) is the technique of choice. Nitrous oxide (70%) and oxygen (30%) may be given with contractions, but 100% oxygen should be administered between contractions.

Vaginal delivery is preferred. If the patient is not at term, if labor is not inducible, if she is bleeding or if there is a question of disproportion, cesarean section may be necessary. If so, use procaine (or equivalent) for local infiltration of the abdominal wall. After the baby is delivered, give thiopental (Pentothal®) anesthesia for abdominal closure.

### Prognosis

The maternal mortality rate in eclampsia is 10-15%. Most patients improve strikingly in 24-48 hours with appropriate therapy, but early termination is usually required.

Although babies of mothers with toxemia of pregnancy are small for their gestational age (mainly because of placental malfunction), they fare better than premature babies of the same weight born of nontoxic mothers.

Adams J Q & W B Cameron. Management of eclampsia. *Am J Obst & Gynec* 80:253, 1960.

Mackie M A. Treatment of toxemia of pregnancy. *M J Australia* 1:551-3, 1961.

## ABORTION

### Essentials of Diagnosis

- Vaginal bleeding in a pregnant woman
- Uterine cramping
- Disappearance of symptoms and signs of pregnancy
- Negative or equivocal pregnancy tests
- The products of conception may or may not be expelled

The bleeding which occurs in abortion of a uterine pregnancy must be



differentiated from the abnormal bleeding of an aborting ectopic pregnancy, hyperestrinism in a nonpregnant woman, and membranous dysmenorrhea. The passage of hydropic villi in the bloody discharge is diagnostic of the abortion of a hydatidiform mole.

### General Considerations.

Abortion is defined as termination of gestation before the fetus becomes viable. Viability is usually reached at 28 weeks, when the infant weighs slightly more than 1 Kg. (2 2 lb). About three-fourths of abortions occur before the 16th week of gestation, of these, three-fourths occur before the eighth week. About 12% of all pregnancies terminate in spontaneous abortion, at least 15% of abortions are criminally induced.

About 50-60% of spontaneous abortions result from ovular defects, 15% are caused by maternal factors (trauma, infections, dietary deficiencies, diabetes mellitus, hypothyroidism, poisoning, anatomic malformations). There is no good evidence that abortion may be induced by psychic stimuli such as severe fright, grief, anger, or anxiety. In about one-fourth of cases the cause of abortion cannot be determined.

### Clinical Findings.

**A. Symptoms and Signs** Abortion is classified clinically as (1) complete, (2) incomplete or inevitable, and (3) missed. In threatened abortion the previable gestation is in jeopardy but the pregnancy continues.

**1 Complete abortion** - In complete abortion all of the conceptus is expelled. When complete abortion is impending the symptoms of pregnancy often disappear, sudden bleeding then begins, followed by cramping. The fetus and the rest of the conceptus may be expelled separately. When the entire conceptus has been expelled, pain ceases but slight spotting persists.

**2. Incomplete or inevitable abortion** - In incomplete abortion portions of the conceptus are passed, in inevitable abortion the passage of some or all of the products of conception is momentarily impending. Bleeding and cramps do not subside.

**3 Missed abortion** - In missed abortion the pregnancy has been terminated for at least one month but the conceptus has not been expelled. Symptoms of pregnancy disappear and the BBT is not elevated. There is a brownish vaginal discharge but no free bleeding. Pain is not present. The cervix is semi-firm and slightly patulous, the uterus becomes smaller and irregularly softened, the adnexa are normal.

**B. Laboratory Findings** Pregnancy tests are negative or equivocally positive. Blood and urine findings are those usually observed in infection and anemia if these complications have occurred.

**C. X-ray Findings** In late abortion a plain film of the abdomen may demonstrate a distorted angulated fetal skeleton and often intra-uterine gas.

### Complications.

Hemorrhage in abortion is a major cause of maternal death. Infection is most common after criminally induced abortion, death results from salpingitis, peritonitis, septicemia, and septic emboli. Less common complications are perforation of the uterus, chorio-epithelioma, and infertility.

### Treatment.

**A. Emergency Measures** If abortion has occurred after the first trimester, the patient should be hospitalized. In all cases induce uterine contraction with oxytocics, e.g., oxytocin (Pitocin®), I.M. or I.V. (not ergot preparations), to limit blood loss and aid in the expulsion of clots and tissue. Ergotrate should be given only if the diagnosis of complete abortion is certain. Give antishock therapy, including blood replacement, to prevent collapse after hemorrhage.

**B. General Measures** Place the patient at bed rest and give sedatives to allay uterine irritability and limit bleeding. Coitus and douches are contraindicated. Antibiotics are indicated if criminal abortion is likely or if signs of infection are present.

### C. Surgical Measures

**1 Cerclage** (Shirodkar) during the second trimester for closure of an incompetent internal cervical os.

**2. Dilatation and curettage** for possible retained tissue. Start an I.V. drip of oxytocin (Pitocin®) before surgery to avoid uterine penetration.

**3. Uterine packing** to control bleeding and promote separation and evacuation of fragments. Remove the packing in 6-8 hours to allow drainage.

### Prognosis.

The prognosis is good if severe infection is avoided. If the maternal factors which caused an abortion can be corrected, future pregnancies often go to term without incident.

## HYDATIDIFORM MOLE & CHORIO-EPITHELIOMA

### Essentials of Diagnosis

- Uterine bleeding at 6-8 weeks
- Excessive nausea and vomiting
- Uterus larger than expected for duration of pregnancy
- Presence of vesicles passed from vagina
- Urinary chorionic gonadotropins high

Differentiate from normal pregnancy by excessive increase in size of uterus or the presence of vesicles in the vagina or cervix

### General Considerations

Hydatidiform mole is a degenerative disorder of the chorion which occurs as a complication of about one in 1500 pregnancies in the U S A , usually during the first 18 weeks. It is characterized by prominent pale yellow grape-like vesicular enlargements of the villi and vascular incompetence of the villous tree. Although it is assumed to be of placental (fetal) origin, the precise etiology is not known. Hydatidiform mole is more common among women over 40 and is over 5 times more prevalent in the Orient than in the West. Malignant change (chorio-epithelioma) occurs in about 4% of cases in the U S A and is fatal in 90% when it does occur.

### Clinical Findings

**A Symptoms and Signs** Excessive nausea and vomiting occur in over one third of patients with hydatidiform mole. Uterine bleeding beginning at 6-8 weeks is observed in virtually all instances and is indicative of threatened or incomplete abortion. In about one-fifth of cases the uterus is larger than would be expected in a normal pregnancy of the same duration. Intact or collapsed vesicles may be passed through the vagina.

Eclamptogenic toxemia frequently of the fulminating type may develop during the second trimester.

Chorio-epithelioma may be manifested by continued or recurrent uterine bleeding after evacuation of a mole or by the presence of an ulcerative vaginal tumor, pelvic mass or evidence of distant metastatic tumor. The diagnosis is established by pathologic examination of curettings or by biopsy.

**B Laboratory Findings** Hydatidiform mole or chorio epithelioma is probably present when the FSH exceeds 0.5 million rat units/L

L of urine and the LH titer is above 0.2 million rat units/L. The urinary 17-ketosteroid level is often twice the normal pregnancy level (10-15 mcg /100 ml). The vaginal smear reveals distinct heavy cell groupings, a predominance of superficial cells, acidophilia and pyknosis in about half of the exfoliate cells.

**C X-ray Findings** Hysterography after the third month either by the transcervical or transcutaneous route utilizing I V urographic media may demonstrate a honeycomb appearance of the uterine contents.

**D Specific Examinations** Preserve any tissue passed spontaneously. Identification of placental hydatids will establish the diagnosis.

### Differential Diagnosis

The excessive nausea and vomiting which occurs in hydatidiform mole must be distinguished from hyperemesis gravidarum, the excessively large uterus from multiple pregnancy, hydramnios and uterine tumors and the vaginal bleeding from threatening or complete abortion. The presence of a large uterus, laboratory findings of pregnancy with the absence of a fetal skeleton by x-ray makes the diagnosis of a mole very probable.

### Treatment

**A Emergency Measures** Hemorrhage indicative of abortion requires immediate hospitalization. Type and cross-match the patient's blood and have at least 2 units of blood available for transfusion. Free bleeding will cease as soon as the uterine contents are evacuated and firm uterine contraction with oxytocin is established. Curettage will probably be required for removal of adherent tissue.

#### B Specific (Surgical) Measures

1 Empty the uterus as soon as possible after the diagnosis of hydatidiform mole is established. Spontaneous evacuation followed by careful dilatation and curettage is the preferred method of treatment in 75% of cases. Pack the uterus for 6-12 hours after curettage to reduce bleeding and aid in the removal of tissue missed by the curet. Give ergonovine maleate (Ergostat®) 0.2 mg (1/300 gr) orally every 4 hours after curettage for 4 doses.

2 Hysterotomy - If the uterus is larger than a five-month pregnancy and the cervix is resistant to wide dilatation, hysterotomy is indicated (vaginal if infection is clinically evident, otherwise anterior abdominal). Do not resect ovarian cysts or remove the ovaries.

spontaneous regression will occur with elimination of the mole.

3. Hysterectomy - If malignant tissue is found at surgery or follow-up, total hysterectomy and bilateral salpingo-oophorectomy are indicated. Antitumor doses of radium or x-ray radiation may have to be directed at the site of residual or metastatic cancer (e.g., pelvis, lung). Methotrexate is the most promising chemotherapeutic agent, and may be used in place of x-ray.

C. Supportive Measures: Replace blood and give iron and vitamins. If infection is suspected, give broad-spectrum antibiotics for 24 hours before and 3-4 days after surgery.

#### Prognosis.

The risk of chronic abortion is not great in women who have had hydatidiform mole.

Ninety per cent of patients with chorioepitheliomas die in less than one year despite therapy.

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### THIRD TRIMESTER BLEEDING

Five to 10% of women have vaginal bleeding in late pregnancy. Multiparas are more commonly affected. Obstetric bleeding is the major cause of maternal mortality and morbidity. The physician must distinguish between placental causes of obstetric bleeding (placenta previa, premature separation of the placenta) and nonplacental causes (systemic disease or disorders of the lower genital tract).

In general, the approach to the problem of bleeding in late pregnancy should be conservative and hopeful.

The patient should be hospitalized at once, preferably by ambulance, at complete bed rest. Perform a complete, gentle abdominal examination but no rectal or vaginal examination. Over 90% of patients with third trimester bleeding

will cease to bleed in 24 hours on bed rest alone. If bleeding is profuse and persistent, however, vaginal examination is indicated after preparation and blood replacement. The operating room should be ready for cesarean section before this examination is done.

If the patient is less than 36 weeks pregnant and the fetus is too small for survival, it may be necessary to keep her in the hospital or at home at bed rest until the chances of delivering a viable infant are more favorable. If bleeding stops, it is likely that it will start again.

### POSTPARTUM HEMORRHAGE

Postpartum hemorrhage has been defined arbitrarily as the loss of at least 500 ml. of blood following delivery. However, since a small woman can lose blood less safely than a large one, it is felt that the loss of 1% or more of body weight (expressed in terms of ml. of blood) would be a more useful definition. Postpartum hemorrhage is the major cause of maternal mortality in the U.S.A.

The most common causes are uterine atony, lacerations during delivery, and blood dyscrasias or coagulation defects.

#### Prevention.

The following types of patients are especially prone to develop postpartum bleeding: Women with multiple pregnancies, polyhydramnios, a history of postpartum hemorrhage, primary or secondary uterine inertia, desultory or prolonged labor, uterine infections, placenta previa, abruptio placentae, after heavy analgesia or anesthesia, and those who are delivered by cesarean section. Measures to prevent postpartum bleeding in these patients are as follows:

A. Start 500 ml. of 5% glucose in water slowly I.V. through a No. 18 needle near the end of the first stage of labor.

B. Immediately after delivery, add 0.5 ml. oxytocin (Pitocin®) to the infusion (not into the tubing).

C. On completion of the third stage of labor, give ergonovine maleate (Ergotrate®), 0.2 mg. (1/300 gr.) I.M. Avoid giving excessive amounts of analgesics and anesthesia.

D. Maneuver the uterus up and out of the pelvis and by raising it with a large sponge on

a forceps into the vagina massage it gently until it becomes firm and remains so.

E. Keep the patient in the delivery room or recovery room for one hour after delivery.

#### Treatment.

A. Emergency Measures Control bleeding promptly by suture, manual recovery or expression of the placenta, or I.V. oxytocin (Pitocin®) as indicated. Packing of the uterus (and vagina) controls bleeding by the pressure applied to bleeding points and because packing stimulates uterine contractions. However, packing must be used with discretion for the following reasons (1) The uterus relaxes slowly and bleeding often recurs, even when packing is very tight. (2) Tight packing may actually prevent uterine contractions. (3) If packing fails to check bleeding, further blood loss may make a necessary hysterectomy even more hazardous. (4) The risk of infection is greater with packing than when other methods of hemostasis are used.

B. General Measures Reinspect the placenta for missing fragments. Examine for lacerations of the birth canal. Note the quality of contractions of the elevated uterus, determine bleeding and clotting time, and obtain typed and cross-matched blood for transfusion.

#### Prognosis.

The mortality rate in postpartum hemorrhage depends upon the amount and rapidity of blood loss, the patient's general health, and the speed and adequacy of treatment.

### INVERSION OF THE UTERUS

Inversion of the uterus at or following delivery (puerperal inversion) is an extreme medical and surgical emergency. It may occur as a result of straining, pulling by the infant on the cord and placenta, traction on the cord by the physician before placental separation, severe "kneading" of the fundus (overzealous Credé maneuver), or separation and extraction of an adherent placenta. The incidence is about one in 15,000 deliveries. The diagnosis is obvious.

Nonpuerperal inversion is a less serious disorder which is due to extrusion or associated with extraction of a large uterine tumor (myoma). Treatment consists of hysterectomy if replacement is unsuccessful.

#### Prevention.

Most cases of puerperal uterine inversion can be prevented by good obstetric care. Do not pull on the cord unless the placenta has separated. Do not push on the fundus or use the Credé maneuver. Do not leave the patient until the uterus is contracted and rounded. Do not place a pad or roll beneath the abdominal binder after delivery.

#### Treatment.

Note: Consultation and assistance are mandatory, since maternal mortality is about 30% unless treatment is prompt and appropriate.

A. Emergency Measures Shock (out of proportion to blood loss) must be controlled with I.V. fluids, plasma, whole blood, and oxytocin (Pitocin®). Do not use ergot preparations during this stage of management, since they cause tetanic contractions of the cervix and uterus and interfere with manipulation.

B. Specific Measures Replace the uterus by abdominovaginal manipulation, applying countertraction on the cervix while reinserting the inverted portion. Deep general (ether) anesthesia is required. Leave the placenta attached, compress the fundus in the antero-posterior diameter, and apply ring forceps to the cervix. Combat cervical constriction with amyl nitrite by inhalation or epinephrine, 5-10 min. of 1:1000 solution, I.M. Leave the fist in the uterus and administer ergonovine maleate (Ergotrate®) or ergotamine tartrate (Gyn-ergon®), which at this point have the advantage of causing cervical constriction and thus preventing recurrence after manual support is withdrawn. Packs are contraindicated since they tend to maintain uterine distention.

C. Surgical Measures If manipulative treatment is not immediately successful, proceed at once to surgical correction to avoid infection.

1. Transabdominal replacement (Haultain) - Incise the posterior wall of the inverted uterus, replace the fundus with towel clamps applied hand-over-hand, and suture.

2. Transvaginal replacement - Two methods are available (1) Transect the cervix anteriorly to replace the fundus from below, and suture (Spinelli). (2) Incise through the cervix posteriorly, replace the fundus, and suture (Küstner).

D. Postoperative Measures Give broad-spectrum antibiotics, replace blood, fluids, and electrolytes; and decompress the stomach with a nasogastric tube.

### Prognosis.

Manual replacement, properly performed, is successful in about 75% of patients with inversion. Maternal mortality with inadequate management is about 30%.

Recurrence is not likely, though it is possible.

## URINARY TRACT INFECTION DURING PREGNANCY

Serious infection of the urinary tract occurs in 5-8% of pregnant women antepartum and in about 5% of women after delivery. The usual pathogens, in order of frequency, are *Escherichia coli* (one-third of cases), *Staphylococcus aureus* and *hemolyticus*, *Streptococcus faecalis*, *Pseudomonas aeruginosa*, and *Proteus vulgaris*. Although many cases of infection are merely coincidental with pregnancy, hormonal and physiologic changes leading to congestion of the pelvic tissues and relative urinary stasis are important predisposing factors.

The onset is usually sudden, with intermittent or remittent fever to 39.4-40° C. (103-104° F.), chills, and malaise. Aching pain in the flank or in the costovertebral angle (more severe on the involved side) usually appears early. Dysuria, urgency, and frequency are common early complaints. The urine is smoky or frankly bloody in about 15% of cases, bleeding often occurs at the termination of voiding. Abdominal pain, often with ileus, may be of renal or ureteral origin. The signs and symptoms of premature labor (uterine contractions) may be described early in the course of the urinary tract infection. Marked leukocytosis usually is present.

About 60% of cases of acute pyelonephritis during pregnancy are diagnosed incorrectly at first. The most common misdiagnoses are premature labor, false labor, renal colic, gastroenteritis, and appendicitis.

Fever is often absent even in patients with fulminating acute urinary tract infection during pregnancy. The endotoxin of *Escherichia coli* may actually cause hypothermia for several days in well-established cases of pyelonephritis.

Place the patient at complete bed rest, encourage her to lie on alternate sides to promote drainage of urine. Force fluids to 4 L./day. Alkalinize urine. Although the infective organism can be eradicated in 80-90% of cases within a week by means of appropriate antibiotics, reinfection with drug-resistant bacteria either of a different strain or a different species occurs in most cases.

Avoid catheterization whenever possible; when catheterization is necessary, technique must be sterile. Eradicate genital and urinary tract infections promptly. Study and treat patients before or early in pregnancy when there is evidence or a history of a previous urinary tract infection, especially during gestation. Even if a "cure" is achieved, suppressive long-term antibiotic therapy continued through pregnancy and the puerperium should be considered.

## SURGERY DURING PREGNANCY

Elective major surgery should be avoided during pregnancy. However, normal, uncomplicated pregnancy has no debilitating effect and does not alter operative risk except as it may interfere with the diagnosis of abdominal disorders and increase the technical problems of intra-abdominal surgery. Abortion is not a serious hazard after operation unless peritoneal sepsis or other significant complication occurs.

During the first trimester, congenital anomalies may be induced in the developing fetus by hypoxia. It is preferable to avoid surgical intervention during this period, if surgery does become necessary, the greatest precautions must be taken to prevent hypoxia and hypotension.

The second trimester is usually the optimum time for operative procedures.

### Appendicitis During Pregnancy.

Appendicitis occurs in about one of 1200 pregnancies. Management is more difficult than when the disease occurs in nonpregnant persons since the appendix is carried high and to the right, away from McBurney's point, any localization of infection does not usually occur. The distended uterus displaces the colon and small bowel, uterine contractions prevent abscess formation and walling-off; and the intestinal relationships are disturbed. In at least 20% of obstetric patients, the correct diagnosis is not made until the appendix has ruptured and peritonitis has become established. Delay may lead to premature labor or abortion.

Early appendectomy is indicated. If the diagnosis is made during labor at or near term, do an extraperitoneal cesarean section and appendectomy to minimize peritonitis. Therapeutic abortion is never indicated with appendicitis. If drains are necessary, they should be transabdominal, not transvaginal.

With early diagnosis and appendectomy, the prognosis is good for the mother and her baby.

## SUPPRESSION OF LACTATION

If the patient does not wish to suckle her infant and wishes to "dry up" her breasts, this can be done by estrogen or androgen administration or by mechanical inhibition of lactation. Hormones presumably suppress lactation by inhibiting the secretion of pituitary hormone. Hormonal suppression is effective only if started immediately after delivery.

## Suppression With Estrogens.

A Oral estrogen e.g. ethinyl estradiol 1.3 mg (26 tablets containing 0.05 mg each), administered as follows (Diethylstilbestrol may be used in comparable doses)

- 1 Four tablets (0.2 mg) b.i.d. on the first postpartum day
- 2 Three tablets (0.15 mg) b.i.d. on the second day
- 3 Two tablets (0.1 mg) b.i.d. on the third day
- 4 One tablet (0.05 mg) b.i.d. on the fourth through the seventh days

B Depot Estrogens Estradiol valerate (Delestrogen®) 3 ml of a solution containing 10 mg/ml immediately after delivery

## Suppression With Androgens.

Methyltestosterone, 10 mg buccal tablets dissolved in the cheek pouch 5 times daily on the second and third postpartum days

## Suppression With Estrogens &amp; Androgens

Testosterone enanthate, 90 mg/ml, and estradiol valerate 4 mg/ml, 3 ml injected immediately after delivery

## Mechanical Suppression of Lactation.

If the patient begins to nurse and then for any reason wishes to transfer her baby to formula feedings and dry up her breasts (e.g., if mastitis develops or the baby is to be weaned) hormones will not be effective and mechanical suppression is indicated. The patient should cease attempting to nurse and should not express milk or pump her breasts. Apply a tight compression "uplift" binder for 72 hours and a snug brassiere thereafter. Ice packs and analgesics e.g. aspirin and codeine, can be used as necessary. Fluid restriction and laxatives are of no value.

The breasts will become distended, firm, and tender. After 48-72 hours, lactation will cease and pain will subside. Involution will be complete in about one month.

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## The Rheumatic Disorders

Ephraim P. Engelman

### Examination of the Patient

The examination of the patient with rheumatic disease should include a careful history and physical examination, with special emphasis on determining the functional status of the joints (e.g., range of motion, ankylosis, deformity, atrophy). Complete blood count, urinalysis, erythrocyte sedimentation rate, and x-rays of one or more of the involved joints are usually essential to complete the diagnostic picture. Additional studies may include determination of the serum uric acid, aspiration and examination of joint fluids, and tests for the rheumatoid factor and other abnormal globulins. These studies are important from a diagnostic standpoint and also serve as a base-line for planning the therapy and evaluating the clinical progress of the patient.

### Examination of Joint Fluid

Synovial fluid examination provides valuable diagnostic and prognostic information in the management of joint disease since it demonstrates the severity of synovial tissue inflammation. The skin overlying the joint to be aspirated is cleansed with soap and water and then prepared with an antiseptic solution. With sterile technic the puncture site is infiltrated with a local anesthetic. The knee, by far the easiest joint to tap, is entered with an 18 gauge needle slightly superior and 2 cm. (3/4 inch) lateral (or medial) to the patella with the joint fully extended. From this position the suprapatellar space is entered. After removal of as much fluid as possible, the needle is withdrawn and the puncture site covered with a sterile bandage or adhesive dressing.

The following studies should then be performed:

(1) Careful note of the consistency and appearance of the fluid

(2) Cell count. Collect 2-3 ml. in an oxalated bottle (to prevent clotting). The red and white cells are counted, using the same

equipment and technic as for a standard WBC. The diluent, however, should be normal saline since the usual acidified diluent causes the fluid to clot in the pipet (see below). One drop of methylene blue added to the saline makes the cells distinguishable. Differential counts are performed on thin smears with Wright's stain.

(3) Mucin clot test. A small amount of fluid is placed in a test tube and enough acetic acid is added to make a final concentration of about 1% or more. The clot is graded from good to very poor according to its integrity (see chart on p. 412).

(4) Culture. Collect 1 ml. of fluid in a sterile culture tube and perform routine cultures as well as special studies for tubercle bacilli or fungi as indicated.

(5) Sugar. Collect 2-3 ml. of fluid in a fluoride tube. The patient must be fasting, and the blood sugar must be determined at the time of joint fluid aspiration.

**Interpretation.** Synovial fluid studies are not diagnostic unless a specific organism is identified in the culture. As shown in the chart on p. 412 there is considerable overlap in the cytologic and biochemical values obtained in different diseases. These studies do, however, make possible differentiation (according to the severity of inflammation) into "septic" and "traumatic" types. "Septic" joint fluids (including those which occur in rheumatoid arthritis and the infectious arthritides) are often turbid with an elevated WBC (usually well above 3000 cells/cu mm., with over 50% polymorphonuclear forms), a poor mucin clot, and a synovial fluid sugar content which is considerably lower than the blood sugar. The "traumatic" group of diseases (including osteoarthritis, traumatic arthritis, and neuroarthropathy) usually produce a clear fluid with a low WBC (usually below 3000/cu mm.) and a good mucin clot, and the synovial fluid and blood sugar levels are within 10 mg./100 ml. of each other.

## COMMON JOINT DISEASES

## RHEUMATOID ARTHRITIS

## Essentials of Diagnosis

- A systemic disease
- Prodromal symptoms common: malaise, fever, weight loss, sweating or paresthesias (or both) of hands and feet Raynaud's phenomenon, morning stiffness
- Onset usually insidious and in small joints of hands and feet, progression is centripetal and symmetric, deformities common
- Other extra-articular signs: atrophy of skin and muscle, lymphadenopathy, subcutaneous nodules, splenomegaly, iritis
- Serologic tests for rheumatoid factor often positive

Chronic rheumatoid arthritis must be distinguished from allied diseases of connective tissue, notably systemic lupus erythematosus, and from osteoarthritis, chronic tophaceous (gouty) arthritis, and tuberculous arthritis. Acute episodes of rheumatoid arthritis must be distinguished from rheumatic fever, acute gouty arthritis and pyogenic arthritis.

## General Considerations.

Rheumatoid arthritis is a chronic, systemic inflammatory disease of unknown etiology. The incidence in the general population is 2-3%, female patients outnumber males almost 2:1. The usual age at onset is 20-40 years, the disease is relatively uncommon in children. Psoriasis is seen in slightly over 5%.

The pathologic findings in the joint include chronic synovitis with pannus formation. Cartilage erosion occurs early. In the acute phase, effusion and other manifestations of inflammation are common. In the late stage

Significant Synovial Fluid Findings in Common Joint Diseases\*

	Appearance	Clot	Range†	Leukocytes (/cu mm)	Poly %	Type of Mucin‡	Sugar Differences§ (mg./100 ml)
Normal	Clear	0	min aver max.	13 63 180	0 7 25	G G G	< 10
Traumatic arthritis	Clear	0 +	min. aver. max.	50 1250 10 400	0 5 36	F G G	-4 5 24
Osteoarthritis (degenerative joint disease)	Clear to sl turbid	0 ++	min. aver. max.	70 720 8600	0 7 58	F G G	-6 0 17
Rheumatic fever	Sl turbid	0 +++	min. aver. max.	300 17 820 98 200	2 50 88	F G G	-5 4 9
Gouty arthritis	Turbid	± +++	min. aver. max.	1000 13,317 70,600	0 71 99	VP P G	-12 12 74
Rheumatoid arthritis	Clear to turbid	0 +++	min. aver. max.	450 14 000 66 000	0 65 96	VP P G	-14 26 87
Tuberculous arthritis	Turbid	0 +++	min. aver. max.	2500 19,470 105 000	18 60 96	VP P G	-3 60 108
Specific infectious arthritis	Very turbid	0 +++	min. aver. max.	7800 73,370 268,000	46 90 100	VP VP F	-40 71 122

\*Modified from M.W. Ropes, Bull Rheum Dis 7(supplement):22, 1957

†The values to the right of this column indicate the ranges found min. = minimum, aver. = average, max. = maximum.

‡VP = few flecks in cloudy solution, P = small friable mass in cloudy solution, F = soft mass in clear or slightly cloudy solution, G = tight,ropy clump in clear solution.

§The difference between serum and fluid concentrations.



organization may result in fibrous ankylosis; true bony ankylosis is occasionally seen. In both acute and chronic phases, inflammation of soft tissues around the joints may be prominent. Granulomatous invasion of adjacent bone with resulting bony destruction may occur.

The most characteristic histologic lesion of rheumatoid arthritis is the subcutaneous nodule. This is a granuloma with a central zone of necrosis, a surrounding palisade of radially arranged elongated connective tissue cells, and a periphery of chronic granulation tissue. Pathologic alterations indistinguishable from those of the subcutaneous nodule are occasionally seen in the myocardium, pericardium, endocardium, heart valves, visceral pleura, lungs, sclera, dura mater, spleen, and larynx, as well as in the synovia, periarticular tissues, and tendons. Nonspecific pericarditis is found in 25-40% of autopsied patients. Additional nonspecific lesions include inflammation of small arteries, round cell infiltration of skeletal muscle and perineurium, and hyperplasia of lymph nodes. Secondary amyloidosis is found in 20% or more of autopsied patients.

### Clinical Findings

**A Symptoms and Signs** The onset of articular signs of inflammation is usually insidious, with prodromal symptoms of malaise, weight loss, vasomotor disturbances (e.g., paresthesias, Raynaud's phenomenon), and vague articular pain or stiffness. Less often, the onset is acute, apparently triggered by a stressful situation such as infection or trauma. In any case there is characteristically symmetric joint swelling with associated stiffness, redness, warmth, tenderness, and pain. Pain and stiffness are prominent in the morning and subside during the day with moderate use, but are much more severe after strenuous activity. Although any joint may be affected, the proximal interphalangeal and metacarpophalangeal joints of the fingers, wrists, knees, ankles, and toes are most often involved. Monarticular disease is occasionally seen early, especially in children. Palmar erythema is seen occasionally. Twenty per cent of patients have subcutaneous nodules. These are most commonly situated over bony prominences, but are also observed in the bursae and tendon sheaths. Five to 10% of patients have an enlarged spleen, and about 30% have lymph node enlargement. Low-grade fever, anorexia, weight loss, fatigue, and weakness are often present, chills do not occur except in children with severe disease. After months or years, thickening of the periarticular tissue, flexion

deformities, subluxation, and ankylosis may occur. Atrophy of skin or muscle is common. Nongranulomatous iritis may occur. Heart disease, when present, is frequently unsuspected clinically and found only at autopsy.

**B Laboratory Findings** Serum protein abnormalities are often present. Various serologic techniques are used to detect certain macroglobulins which constitute the so-called rheumatoid factor. One of these, the F2 latex fixation test, is positive in 60-75% of cases. False-positive reactions are not unusual, especially with liver disease and syphilis and in symptom-free relatives of patients with rheumatoid arthritis. During both the acute and chronic phases the C-reactive protein and the ESR are elevated. A moderate hypochromic normocytic anemia is common. The WBC is normal or slightly elevated, but leukopenia may occur especially in the presence of splenomegaly. Joint fluid examination is valuable, reflecting abnormalities which are associated with varying degrees of inflammation.

**C X-ray Findings** Early signs are osteoporosis around the involved joint and erosion of the cartilage at the periphery of the joint surface. Later, extensive erosion of cartilage produces joint space narrowing. Bony cysts result from invasion by granulation tissue. After some years the degenerative changes of secondary osteoarthritis may be superimposed.

### Differential Diagnosis

The differentiation of rheumatoid arthritis from other diseases of connective tissue can be exceedingly difficult, even impossible. However, certain clinical features are often helpful. Rheumatic fever is characterized by the migratory nature of the arthritis, the dramatic and objective response to salicylates in adequate dosage, the more common occurrence of carditis, and the elevated antistreptolysin titer. Butterfly rash, positive L.E. preparations, and renal disease point to the diagnosis of systemic lupus erythematosus. Osteoarthritis is not associated with constitutional manifestations and the joint pain of the latter is characteristically relieved by rest, in striking contrast to the morning stiffness of rheumatoid arthritis. Signs of articular inflammation, prominent in rheumatoid arthritis, are usually minimal in osteoarthritis. Gouty arthritis may be confused with rheumatoid arthritis, but acute onset in one joint, hyperuricemia, the presence of tophi, and the dramatic response to colchicine are helpful in diagnosis. Pyogenic arthritis can be distinguished by frank chills as well as fever, the

Diagnostic Characteristics of the Major Features of Arthritis

	Rheumatoid Arthritis	Arthritis Due to Specific Infection	Osteoarthritis	Arthritis Due to Gout
Family history of similar illness	Yes	No	Yes	Yes
Past history	No	Specific infection	May be history of joint traumas	No
Sex incidence	Most common in women	Either sex	Either sex	Usually men
Age at onset	Any age but usually 20-40	Any age	Usually over 40	Usually over 35
General physical status	Fair	Acute good Chronic may be poor	Good but may show other senile changes	Good
Type of onset	Insidious (subacute) usual Acute atypical	Acute infection sudden Chronic infection slow	Insidious (slow)	Sudden (cessation of symptoms also sudden)
Fever	Yes	Yes (especially acute)	No	Yes (during acute episodes)
Chills	Only in children	Yes	No	No
Joints involved	Any often symmetric tendency to spread centripetally Especially proximal finger joints	Any usually monoarticular	Usually the large and weight bearing joints also distal joints of fingers	Any mono or polyarticular Especially metatarsophalangeal joint of great toe
Periarticular swelling	Yes	Yes	No	Yes
Ankylosis	Yes	Yes		
Muscle atrophy	Yes	Yes	Yes (local)	Yes (late)
Deformities	Yes	Yes (pyogenic)	No	Yes (late)
Skin changes	Atrophic glossy over joints	Similar to rheumatoid arthritis	Senile changes	Local desquamation and pruritus with recovery from acute attack
Subcutaneous nodules	Yes	No	No	Yes (tophi with urate crystals)
Anemia	Yes	No (early) yes (chronic)	No	No
Leukocytosis	May be present	May be present	No	May be present during acute episode
Sedimentation rate or C reactive protein	Elevated	Elevated	Normal	Elevated
Joint fluid	Nonpurulent (sterile)	Purulent or nonpurulent	Nonpurulent (sterile)	Nonpurulent (sterile)
X ray appearance of joints	Early generalized decalcifications of bone joint effusion Late narrowing of joint spaces bone destruction ankylosis	Similar to rheumatoid arthritis but changes appear much faster and bony decalcification more prominent near involved joints	No changes until late lipping osteophytes and narrowing of joint spaces	Early normal Late punched out radiolucent areas of epiphyseal bone not necessarily diagnostic
Other diagnostic features	Positive rheumatoid agglutination tests (latex ben tonite)	Bacteriologic evidence of specific infection	None	Serum uric acid > 6 mg /100 ml Prompt relief of acute episode by colchicine

demonstration of the causative organism in the joint fluid and the frequent presence of a primary focus elsewhere, e.g., gonococcal urethritis

### Treatment

**A Basic Program (Conservative Management)** All evidence indicates that conservative management offers a long-term prognosis at least no worse than that of more spectacular methods. Since none of these latter measures are curative and because their administration is often accompanied by undesirable side effects, a conservative approach is the method of choice.

The primary objectives of treatment of rheumatoid arthritis are the reduction of inflammation and pain, preservation of function and prevention of deformity. A simple regimen consisting of rest, physical therapy and salicylates is the best means of rehabilitating the patient without trading existing problems for others which may be even more devastating. In any event, these measures are so basically necessary as to warrant their continuation even when more heroic steps must be taken. In other words, these measures constitute the basic program of treatment to which other treatment may be added if necessary.

**1 Systemic rest** - There is a great deal of empirical evidence for the benefits of systemic rest. That rheumatoid arthritis is a systemic disease and not a disease limited to the joints has been shown above. Rest may be considered a common therapeutic denominator treating as it does the person as a whole. Rest in some measure should be prescribed upon diagnosis of active disease.

The amount of rest required depends upon the severity of the disease. Complete bed rest may be desirable and even imperative particularly in patients with profound systemic and articular involvement. In mild disease 2-4 hours of rest each day may suffice, allowing the patient to continue his work by restricting only his avocational activities. The duration of the rest program depends upon the course. In general rest should be continued until significant improvement is sustained for at least 2 weeks, at which time the program may be liberalized. However, the increase of physical activity must proceed gradually and with appropriate support for any involved weight-bearing joints. Recrudescence of the disease is an indication for retarding the rate of physical restoration.

**2 Emotional rest** - The importance of emotional factors in rheumatoid arthritis and the need for psychological support cannot be overemphasized. This support depends upon

rapport between the patient and his doctor. An understanding of the patient's personality and his emotional reactions to his illness (and to all the exigencies of his life) allows the doctor to guide him in his present problems and to anticipate many others.

**3 Articular rest** - Decrease of articular inflammation may be expedited by articular rest. Articular rest is accompanied by bed rest in the case of weight-bearing joints but is further enhanced by appropriate adjustable orthopedic supports or splints. These are of particular value in the presence of deformity, whether due to muscle spasm or soft tissue contracture. Splints not only provide rest for inflamed joints but also relieve spasm and thus pain and also prevent deformities or reduce deformities already present. They must be removable to permit daily motion and exercise of the affected extremities (see below). When ambulation is started, care must be taken to avoid weight-bearing which will aggravate flexion deformities. This is accomplished with the aid of supports such as crutches and braces until the tendency to contracture has subsided.

**4 Exercise** - This is the most important modality in the physical therapy of rheumatoid arthritis. The management of rheumatoid arthritis is based on the concomitant administration of rest and therapeutic exercise always in proper balance. Therapeutic exercises are designed to preserve joint motion and muscular strength and endurance. Most effective are exercises of the active-assistive type. These should be performed within the limits of pain tolerance from the outset of management. As tolerance for exercise increases and the activity of the disease subsides, progressive resistive exercises may be introduced. (Specific instructions for exercises may be obtained in the booklet,

Home Care in Rheumatoid Arthritis, published by the Arthritis & Rheumatism Foundation.)

**5 Heat** - This is used primarily for its muscle-relaxing and analgesic effect. Radiant or moist heat is generally most satisfactory. The ambulatory patient will find warm tub baths most convenient. Exercise may be better performed after exposure to heat.

**6 Salicylates** - Acetylsalicylic acid and sodium salicylate are the analgesic drugs of choice. The proper dose is that amount which provides for optimal relief of symptoms without causing toxic reactions. Most adults can tolerate daily doses of 4-6 Gm (60-90 gr). Tinnitus and gastric irritation are early manifestations of toxicity. If tinnitus occurs, the daily dose should be decreased by decrements

of 0.6 or 0.9 Gm. until this symptom disappears. The addition of antacids may lessen symptoms of gastric irritation. This may also be accomplished by the use of enteric-coated tablets, but enteric coating may interfere with the absorption of salicylates.

7 Acetophenetidin (phenacetin) - Occasionally it is helpful to replace part or all of the salicylates with phenacetin. The daily dose should not exceed 2 Gm. (30 gr.)

8 Other analgesic drugs - It may be necessary to supplement salicylates and phenacetin with such drugs as dextro propoxyphene (Darvon®) 60-120 mg. every 6-8 hours as needed or with ethoheptazine citrate 75 mg. and aspirin 300 mg. (5 gr.) (Zactirin®) 1-2 tablets every 6-8 hours as needed. Codeine and other narcotics should not be used.

9 Diet - The diet should be well balanced and adjusted to each individual's requirements. There is no specific food contraindication. If dietary intake is normal there is usually no need to use supplemental vitamins.

10 Hematinic agents - These are not beneficial in the treatment of the anemia of rheumatoid arthritis. In the presence of coexisting iron deficiency, however, iron salts, e.g., ferrous sulfate, 0.2 Gm. (3 gr.) orally *t.i.d.*, are useful.

**B Corticoids** (Cortisone, hydrocortisone, prednisone, prednisolone, triamcinolone, methylprednisolone, dexamethasone) - These agents represent an important advance in the management of rheumatoid arthritis. However, they must be considered as a supplement to and not a substitute for the comprehensive approach outlined above. Perhaps the greatest disadvantage which might stem from their use, aside from the serious problem of untoward reactions, lies in the tendency of patient and physician to neglect the less spectacular but proved benefits which may be derived from general supportive treatment, physical therapy and orthopedic measures. These agents do not represent the long-awaited 'specific' anti-rheumatic factor and do not cure the disease. While corticoids usually produce immediate and dramatic symptomatic relief, they do not alter the natural progression of the disease, furthermore, clinical manifestations of active disease commonly reappear when the drug is discontinued.

1 Indications - Active and progressive disease which does not respond favorably to conservative management, patients who should not receive gold salts.

2 Relative contraindications - Peptic ulcer, active infection, hypertension, diabetes mellitus.

3 Daily oral dose - Give the least amount which will permit functional improvement but not more than 10-15 mg. of prednisone or equivalent. Efforts should be made every 3 or 4 weeks to lower the daily dose.

4 Intra-articular corticoids (hydrocortisone acetate or other) may be helpful if one or 2 joints are the chief source of difficulty. Intra-articular hydrocortisone in a dose of 25-50 mg. may be repeated as required for symptomatic relief.

**C Gold Salts (Chrysotherapy)** - Although the value of gold salts in the treatment of rheumatoid arthritis remains highly controversial, this form of therapy has regained some of its former popularity in recent years. The mode of action is not known.

1 Indications - Active disease responding unfavorably to conservative management, patients who should not receive corticoids.

2 Contraindications - Previous gold toxicity, other drug allergy, systemic lupus erythematosus (misdiagnosed as rheumatoid arthritis), significant renal, hepatic, or hematopoietic dysfunction, general debility.

3 Preparations of choice - Gold thiomalate or gold thioglucose.

4 Weekly 1 M dose - 10 mg. the first week, 25 mg. the second week, and 50 mg. weekly thereafter until toxic reactions appear, response is adequate or a total dose of 1 Gm. has been given without improvement. If response is good, continue to give 50 mg. every 2 weeks and as improvement continues, every 3 and then every 4 weeks for an indefinite period.

5 Toxic reactions - About 37% of all patients (range in various series 8-61%) experience toxic reactions to gold therapy, the mortality is about 0.4%. The manifestations of toxicity are similar to those due to poisoning with other heavy metals (notably arsenic) and include dermatitis (mild to exfoliative), stomatitis, agranulocytosis, purpura, hepatitis, nitritoid reactions, bronchitis, aplastic anemia, peripheral neuritis, nephritis, and photosensitization. In order to prevent or reduce the severity of toxic reactions, do not give gold salts to patients with any of the contraindicating disorders listed above and observe all patients carefully during the course of gold therapy. Before each injection, ask the patient how he has felt since the previous injection, examine the skin and mucous membranes for dermatitis or purpura, and examine the urine for protein and microscopic hematuria. Every 2 weeks, determine the hemoglobin, WBC, and differential white count values. When indicated, perform platelet

counts or liver function tests Warn the patient against exposure to strong light

If signs of toxicity appear, withdraw the drug immediately Corticosteroids or corticotropin control most toxic reactions Dimer-caprol (BAL) is rarely indicated

**D Chloroquines** It appears probable that chloroquine phosphate and hydroxychloroquine sulfate have mild antirheumatic properties in selected patients with mild rheumatoid arthritis However, toxic reactions occur in as many as 30-40% of patients nausea, vomiting, leukopenia, rash, blanching of hair, ocular disturbances, and toxic psychosis The advantages of these drugs do not appear to justify their clinical use in rheumatoid arthritis

**E Phenylbutazone (Butazolidin®)** This analgesic drug is of limited usefulness in peripheral rheumatoid arthritis (see Ankylosing Spondylitis, below)

### Prognosis

The course of rheumatoid arthritis is totally unpredictable, although spontaneous remissions and relapses are common early in the disease Occasionally, in well-established cases, permanent spontaneous remission occurs with either return to normal function of the involved joints (if involvement is early and minimal) or some decrease in the amount of disability (if of a longer duration) In most cases however, the disease is ultimately progressive some degree of deformity is the usual end result of the disease In 10 years 15% are likely to be bedridden 50% capable of self care and employable, and 35% ambulatory but unable to earn a living

Short, C.L., Bauer, W., & W.E. Reynolds  
Rheumatoid Arthritis Harvard, 1957

Symposium on Rheumatoid Arthritis J Chronic Dis 5 609-778, 1957

## ANKYLOSING SPONDYLITIS (Rheumatoid Spondylitis, Marie-Strümpell Disease, Rheumatoid Arthritis of Spine)

### Essentials of Diagnosis

- Recurrent backache in a young man
- Progressive limitation of back motion and chest expansion
- Transient (50%) or permanent (25%) peripheral joint involvement indistinguishable from peripheral rheumatoid arthritis
- Diagnostic x-ray changes in sacroiliac joints
- Uveitis in 5-10%
- Accelerated sedimentation rate and negative serologic tests for rheumatoid factor

Ankylosing spondylitis must be distinguished from the painful back of disk and bone disease, osteoarthritis, sprain, osteoporosis and tumor

### General Considerations

Ankylosing spondylitis is a chronic inflammatory disease of the joints of the axial skeleton manifested clinically by pain and progressive stiffening of the spine It is felt by many to be a variant of rheumatoid arthritis While the synovitis of ankylosing spondylitis is histologically identical with the synovitis of peripheral rheumatoid arthritis certain features tend to distinguish this disease from rheumatoid arthritis its preponderance among males (approximately 10:1), age at onset (usually in late teens or early 20s) the relatively high incidence of uveitis, a pathologically distinctive lesion of the aorta and the absence of the rheumatoid factor In addition to the synovitis a second pathologic feature of ankylosing spondylitis involves the intervertebral fibrocartilages the annulus fibrosus may gradually ossify with resulting fusion of the vertebral bodies

### Clinical Findings

**A Symptoms and Signs** The onset is usually gradual, with intermittent bouts of back pain which may radiate down the thighs As the disease advances, symptoms progress in a cephalad direction and back motion becomes limited, with the normal lumbar curve flattened and the thoracic curvature exaggerated Atrophy of the trunk muscles is common Chest expansion is often limited as a consequence of costovertebral joint involvement Radicular symptoms may occur In advanced

cases the entire spine becomes fused, allowing no motion in any direction. Transient, acute arthritis of the peripheral joints occurs in about 50% of cases, and permanent changes in the peripheral joints, most commonly in the hips and shoulders, are seen in about 25%. There is increasing awareness of cardiac involvement, aortic incompetence is reported in about 4%. Nongranulomatous uveitis is seen in 5-10% of cases and may be a presenting feature. Constitutional symptoms similar to those of rheumatoid arthritis may occasionally be present.

**B Laboratory Findings** The sedimentation rate is accelerated in 85% of cases, but serologic tests for the rheumatoid factor are usually negative. There may be leukocytosis and anemia.

**C X-ray Findings** The x-ray shows early erosion and sclerosis of the sacroiliac joints with later involvement of the apophyseal joints of the spine, calcification of the anterior and lateral spinal ligaments, and generalized demineralization of the vertebral bodies. The term "bamboo spine" has been used to describe the late radiographic changes.

#### Differential Diagnosis

Although peripheral rheumatoid arthritis may ultimately show involvement of the spine, it is characteristically in the cervical region while the sacroiliac joints are spared. Other features which differentiate ankylosing spondylitis from peripheral rheumatoid arthritis are the absence of subcutaneous nodules and the negative serologic tests for the rheumatoid factor. The history and physical findings of ankylosing spondylitis serve to distinguish this disorder from other causes of low back pain such as degenerative disk disease, osteoarthritis, osteoporosis, soft tissue trauma, and tumors. The single most valuable distinguishing sign of ankylosing spondylitis is the x-ray appearance of the sacroiliac joints, although a similar x-ray picture may be seen as a sequel to Reiter's syndrome, especially after frequent recurrences. The x-ray appearance of the sacroiliac joints in spondylitis should be distinguished from that in osteitis condensans ilii. In some areas and occupations, brucellosis and fluoride poisoning may be important in the differential diagnosis.

#### Treatment.

**A. Basic Program** As for rheumatoid arthritis.

**B Medical Treatment** Phenylbutazone (Butazolidin®) is a potent analgesic which is often remarkably effective against ankylosing spondylitis in small doses and may be used cautiously if response to salicylates is inadequate. It is contraindicated in peptic ulcer, cardiac decompensation, and significant renal, hepatic, or hemopoietic dysfunction. Give the least amount which will provide symptomatic improvement. Start with 100 mg daily and increase if necessary to 100 mg every 12 hours or every 8 hours, but do not give more than 300 mg daily. The drug may be continued cautiously as long as required for symptomatic relief unless toxic reactions occur. Special precautions include blood counts twice weekly for 4 weeks, once weekly for the next 4 weeks, and once every 3 or 4 weeks thereafter.

Toxic reactions include salt and water retention, rash, agranulocytosis and other hematologic abnormalities, peptic ulcer, and hepatitis. If toxicity occurs, withdraw the drug immediately. Corticosteroids or corticotropin may be helpful in the treatment of agranulocytosis.

**C X-ray therapy**, administered to painful areas of spine, often provides symptomatic relief.

**D. Corticoids** may be given as for rheumatoid arthritis.

#### Prognosis

Spontaneous remissions and relapses are common and may occur at any stage. Occasionally the disease progresses to ankylosis of the entire spine. In general, the functional prognosis is good except in those instances where the hips are seriously and permanently involved.

Blumberg, B., & C. Ragan. The natural history of rheumatoid spondylitis. *Medicine* 35 1-31, 1956.

## OSTEOARTHRITIS (Degenerative Joint Disease)

### Essentials of Diagnosis

- A degenerative disorder without systemic manifestations
- Pain relieved by rest
- Articular inflammation minimal
- X-ray findings Narrowed joint space, osteophytes, increased density of subchondral bone, bony cysts
- Commonly secondary to other articular disease

Absence of systemic manifestations and minimal articular inflammation distinguish osteoarthritis from most other arthritides. X-ray evidence of osteoarthritis does not necessarily establish the cause of symptoms, other diseases commonly coexist.

### General Considerations.

Osteoarthritis is a chronic, progressive arthropathy which is characterized by degeneration of cartilage and by hypertrophy of bone at the articular margins. It is traditionally differentiated into 2 types: (1) primary osteoarthritis, which most commonly affects the terminal interphalangeal joints (Heberden's nodes), the metacarpophalangeal and carpometacarpal joints of the thumb, hip (malum coxae senilis), knee, the metatarsophalangeal joint of the big toe, and the cervical and lumbar spine, and (2) secondary osteoarthritis (clinically similar, but often more severe), which may occur in any joint as a sequel to articular injury resulting from either intra-articular or extra-articular causes. The injury may be acute, as in a fracture, or chronic as that due to overweight, bad posture, and occupational overuse of a joint. Pathologically the articular cartilage is first roughened and finally worn away, and spur formation and lipping occur at the edge of the joint surface. The synovial membrane becomes thickened, with hypertrophy of the villous processes, the joint cavity, however, never becomes totally obliterated, and the synovial membrane does not form adhesions. Inflammation is characteristically minimal.

### Clinical Findings

**A. Symptoms and Signs** The onset is insidious. Initially there is articular stiffness which develops later into pain on motion of the affected joint and is made worse by prolonged activity and relieved by rest. Deformity may be absent or minimal, however, bony enlarge-

ment is occasionally prominent. There is no ankylosis, but limitation of motion of the affected joint or joints is common. Coarse crepitus may often be felt in the joint. Joint effusion and other articular signs of inflammation are rare. There are no systemic manifestations.

**B. Laboratory Findings** Elevated sedimentation rate and other laboratory signs of inflammation or dysproteinemia are not present.

**C. X-ray Findings** X-rays may reveal narrowing of the joint space, sharpened articular margins, osteophyte formation and lipping of marginal bone, and damaged and thickened, dense subchondral bone. Bone cysts may also be present.

### Differential Diagnosis

Because articular inflammation is minimal and systemic manifestations are absent, osteoarthritis is seldom confused with other arthritides. The neurogenic arthropathy of Charcot is easily distinguished by x-ray and neurologic examination. Osteoarthritis may coexist with any other type of joint disease. Furthermore, one must be cautious in attributing all skeletal symptoms to degenerative changes in joints, especially in the spine, where metastatic malignancy, osteoporosis, multiple myeloma, or other bone disease may coexist.

### Treatment

#### A. General Measures

1. **Rest**—Physical activity which induces physiologic or traumatic strain should be avoided. Occupational or recreational overuse of an affected joint must be prevented. If weight-bearing joints are involved, such weight-bearing activities as climbing stairs, walking, or prolonged standing should be minimized. Postural strain should be corrected. Supports which relieve strain due to pendulous abdomen or breasts should be supplied.

2. **Diet** should be adjusted to meet the patient's needs. Weight reduction for obese patients helps to diminish stress on the joints.

3. **Local heat** in any form is often of some symptomatic value.

**B. Analgesic Drugs** Salicylates (as for rheumatoid arthritis) are indicated for the relief of pain.

**C. Intra-articular corticoids** (as for rheumatoid arthritis) may give transient relief.

**Prognosis.**

Although marked disability is rare, symptoms may be quite severe and limit activity markedly. This is especially true with involvement of the hips, knees, and cervical spine. Although there is no cure, proper treatment may greatly relieve symptoms and thereby improve function.

Tobin, W. J.: Osteoarthritis. *J. Chronic Dis.* 13 495-506, 1961.

**GOUTY ARTHRITIS****Essentials of Diagnosis**

- Acute onset, usually monarticular, involving the metatarsophalangeal joint of big toe in about 50% of cases
- Dramatic therapeutic response to colchicine
- Postinflammatory desquamation and pruritus are pathognomonic
- Hyperuricemia
- Asymptomatic periods between acute attacks
- Urate deposits in bone, cartilage, joints, and other tissues
- Familial disease, 95% males

Acute gouty arthritis must be distinguished from pyogenic arthritis, acute episodes of rheumatoid arthritis, adult rheumatic fever, cellulitis, and acute Heberden's node. Chronic tophaceous arthritis must be distinguished from rheumatoid arthritis.

**General Considerations.**

Gout is a familial metabolic disease associated with abnormal amounts of urates in the body and characterized by an early, recurring acute arthritis, usually monarticular, and a late chronic deforming arthritis.

About 95% of patients with gout are men, usually over 30 years of age. In women the onset is usually postmenopausal. The characteristic histologic lesion is the tophus, a nodular deposit of sodium acid urate crystals and an associated foreign body reaction. This may be found in cartilage, subcutaneous and periarthritic tissues, tendon, bone, the kidneys, and elsewhere. Urates have been demonstrated in the synovial tissue during the acute arthritis, however, the etiology of the acute arthritis remains unknown. The precise relationship of hyperuricemia to acute gouty arthritis is still obscure, since hyperuricemia

may occur in patients who never have gouty arthritis. The mechanism of the late, chronic stages of arthritis is better understood. This is characterized pathologically by tophaceous invasion of the articular and periarthritic tissues, with structural derangement and secondary degeneration (osteoarthritis).

Uric acid kidney stones are present in 10-20% of patients with gouty arthritis. Nephrosclerosis with renal dysfunction is common, so-called "renal gout" or "gouty nephritis," much less common, refers to kidney disease due to tophaceous deposition in the renal parenchyma, chiefly the pyramids.

Typical acute gouty arthritis may accompany other diseases, notably those of the hematopoietic system, e.g., leukemia or polycythemia, where there is excessive breakdown of nucleic acids. Although referred to as "secondary gout," these attacks are clinically indistinguishable from "primary gout." However, a family history of gout is usually not obtained, and tophi are rare.

**Clinical Findings**

**A. Symptoms and Signs.** The acute arthritis is characterized by its sudden onset, frequently nocturnal, either without apparent precipitating cause or following an infection, surgical procedure, or minimal trauma such as caused by ill-fitting shoes. The metatarsophalangeal joint of the great toe is the most susceptible joint, although other joints, especially those of the feet, ankles, and knees are commonly affected. More than one joint may occasionally be affected during the same attack, in such cases the distribution of the arthritis is usually asymmetric. As the attack progresses the pain becomes intense. The involved joints are swollen and exquisitely tender, and the overlying skin tense, warm, and dusky red. Fever, headache, malaise, anorexia, and tachycardia are common. Local desquamation and pruritus during recovery from the acute arthritis are pathognomonic of gout but are not always present. Tophi may be found in the external ears, hands, feet, olecranon, and prepatellar bursae. They are usually seen only after several attacks of acute arthritis.

During the phase of chronic tophaceous arthritis the symptoms are those of progressive functional loss and disability. Gross deformities, due usually to tophaceous invasion, are seen. Signs of inflammation may be absent or superimposed.

**B. Laboratory Findings.** The blood uric acid is practically always elevated unless uricosuric drugs are being given. During an



acute attack the sedimentation rate and WBC are usually elevated. Examination of the material aspirated from a tophus shows the typical crystals of sodium urate and confirms the diagnosis.

**C X-ray Findings** Early in the disease x-rays show no changes, later, punched-out areas in the bone (radiolucent urate tophi) are seen.

### Differential Diagnosis

Once the diagnosis of acute gouty arthritis is suspected it is easily confirmed by the presence of hyperuricemia, dramatic response to full doses of colchicine, local desquamation and pruritus as the edema subsides, positive identification of tophi, and a positive family history. Acute gout is often confused with cellulitis. Appropriate bacteriologic studies should exclude acute pyogenic arthritis.

Chronic tophaceous arthritis may rarely mimic chronic rheumatoid arthritis. In such cases the diagnosis of gout is established conclusively by the demonstration of urate crystals in the contents of a suspected tophus. Biopsy may be necessary to distinguish tophi from rheumatoid nodules. An x-ray appearance similar to that of gout may be found in rheumatoid arthritis, sarcoid, multiple myeloma, hyperparathyroidism, and Hand-Schüller-Christian disease.

### Treatment.

#### A Acute Attack

1 Colchicine is the drug of choice. It should be given as early as possible in the acute attack or during the prodrome to obtain maximum benefit. Give 0.5 mg ( $\frac{1}{120}$  gr) every hour or 1 mg ( $\frac{1}{60}$  gr) every 2 hours until pain is relieved or until nausea or diarrhea appears, and then stop the drug. The usual total dose required is 4-8 mg ( $\frac{1}{16}$ - $\frac{1}{8}$  gr), and the pain and swelling will subside in 24-72 hours. Once the patient knows how much will produce toxic symptoms, the drug should be given in a dose of about 1 mg ( $\frac{1}{60}$  gr) less than the toxic dose.

2 Phenylbutazone (Butazolidin<sup>®</sup>) is a remarkably effective anti-inflammatory agent in acute gout and is the drug of choice when colchicine is poorly tolerated or inadequate. The initial dose is 400 mg, followed by 200 mg every 6 hours until the attack subsides, do not continue for more than 3 days. Toxicity is rarely a problem in such short-term use of phenylbutazone.

3 Corticotropin (ACTH) and the cortisones often give dramatic symptomatic relief in acute episodes of gout, and if given for a sufficient

length of time will control most acute attacks without relapse. However, when corticotropin and cortisone are discontinued shortly after termination of attacks, many patients promptly relapse unless colchicine is given. Since colchicine and phenylbutazone are equally or more effective and provide a more lasting effect, they are preferred.

4 Analgesics - At times the pain of an acute attack may be so severe that analgesia is necessary before colchicine becomes effective. In these cases codeine may be given. Do not give morphine. Cinchophen and neo-cinchophen should not be used because they cause severe liver damage.

5 Bed rest is very important in the management of the acute attack, and should be continued for about 24 hours after the acute attack has subsided. Early ambulation may precipitate a recurrence.

6 Physical therapy is of little value during the acute attack, although hot or cold compresses to the affected joints may make some patients more comfortable.

**B Management Between Attacks** Treatment during symptom-free periods is intended to minimize urate deposition in tissues, which causes chronic tophaceous arthritis, and to reduce the frequency and severity of recurrences. There is increasing evidence that these objectives are in fact attainable.

1 Diet - Rigid diets are nutritionally inadequate and often fail to influence the hyperuricemia or course of the disease. However, in gouty arthritis the restriction of foods high in purine (e.g., kidney, liver, sweetbreads, sardines, anchovies, meat extracts) may be of some importance in preventing progression of the disease. Specific foods or alcoholic beverages which precipitate attacks should be avoided. However, there is little evidence that alcohol in moderation will precipitate attacks or is otherwise harmful in patients with gout. A high liquid intake and, more important, a daily urinary output of 2 L. or more will aid urate excretion and minimize urate precipitation in the urinary tract.

2 Colchicine - The daily administration of colchicine in a dose of 0.5 mg ( $\frac{1}{120}$  gr) tid should be started simultaneously with uricosuric drugs in order to suppress the acute attack which may be precipitated by uricosuric drugs. After several weeks of uricosuric treatment it is usually possible to lower the daily dose of colchicine to 0.5 mg ( $\frac{1}{120}$  gr). There is some suggestion that colchicine even in this small dosage, has preventive value and should be continued indefinitely.

**3 Uricosuric drugs** - These drugs, by blocking tubular reabsorption of filtered urate and reducing the metabolic pool of urates, prevent the formation of new tophi and reduce the size of those already present. Furthermore, when administered concomitantly with colchicine, they may lessen the frequency of recurrences of acute gout. The indications for uricosuric treatment are either the appearance of tophi on physical or x-ray examination or increasing frequency or severity of the acute attacks.

Any one of several uricosuric drugs may be employed.

(1) Probenecid (Benemid®), starting with 0.5 Gm. daily and gradually increasing to 1-2 Gm. daily.

(2) Salicylates, 5-6 Gm. daily.

(3) Sulfapyrazone (Antursne®), starting with 100 mg. daily and gradually increasing to 200-400 mg. daily. In any case the maintenance dose is determined by observation of serum uric acid response or, preferably, the urinary uric acid response. Ideally, one attempts to maintain a normal serum urate level.

**Precautions With Uricosuric Drugs:** It is important to maintain a daily urinary output of 2000 ml. or more in order to minimize the precipitation of uric acid in the urinary tract. This can be further prevented by giving alkalinizing agents to maintain a urine pH of above 6.0. If a significant uricosuric effect is not obtained in the presence of overt renal dysfunction, do not increase the dose of the drug beyond the limits stated above. Avoid using salicylates with any other uricosuric drug, since they antagonize the action of other uricosuric agents.

**C Chronic Tophaceous Arthritis** There is good evidence that in the presence of good renal function tophaceous deposits can be made to shrink in size and occasionally to disappear altogether. The treatment is essentially the same as that outlined for the intervals between acute attacks. Surgical excision of large tophi offers immediate mechanical improvement in selected deformities and may lessen the load on renal function.

#### Prognosis.

Without treatment, the acute attack may last from a few days to several weeks, but proper treatment quickly terminates the attack. The intervals between acute attacks vary up to years, but the asymptomatic periods often become shorter if the disease progresses. Chronic tophaceous arthritis occurs after repeated attacks of acute gout and inadequate treatment.

Although the deformities may be marked, only a small percentage of patients become bedridden. The younger the patient at the onset of disease, the greater the tendency to a progressive course. Destructive arthropathy is rarely seen in patients whose first attack is after age 50.

Talbott, J.H. - The diagnosis and treatment of gout. *M Clin North America* 45:1489-96, November, 1961.

## ACUTE INFECTIOUS (PYOGENIC) ARTHRITIS

### Essentials of Diagnosis

- Sudden onset of acute arthritis, usually monoarticular, most often in large weight-bearing joints and wrists, frequently preceded by migratory arthralgia.
- Frank chills and fever.
- Joint fluid findings often diagnostic.
- Dramatic therapeutic response to appropriate antibiotic.
- Similar infection commonly found elsewhere in body.

Differentiate from acute gouty arthritis, acute episodes of rheumatoid arthritis, adult rheumatic fever, and cellulitis.

### General Considerations.

The pyogenic cocci (gonococcus, meningococcus, staphylococcus, pneumococcus, and streptococcus) are the usual causes of this form of arthritis. The organisms may enter the joints directly, as in local trauma or surgery, or indirectly, by hematogenous spread. In recent years this type of disease has been seen more commonly as a result of the development of resistant strains of organisms, the increasing therapeutic use of intra-articular injections, and the decreasing mortality of premature infants, in whom the incidence of septic arthritis is relatively high. Pathologic changes include varying degrees of acute inflammation with synovitis, effusion, abscess formation in synovial or subchondral tissues, and, if treatment is not adequate, articular destruction.

### Clinical Findings.

**A Symptoms and Signs** The onset is usually sudden, the joint becomes acutely

painful, hot, and swollen, and chills and fever are often present. The large weight-bearing joints and the wrists are most frequently affected. Although only one or two joints are affected, there may be a prodromal period of migratory arthralgia which may last for several days, this is especially true of gonococcal and meningococcal arthritis.

**B Laboratory Findings** Leukocytosis of the synovial fluid may be as high as 100,000/cu mm, with 90% or more polymorphonuclear cells. Synovial fluid sugar is often low. The organisms can usually be demonstrated by smear or culture. (A notable exception is gonococcal arthritis which can be identified bacteriologically in only one-half of cases.) Other laboratory findings of the infectious disease are present also.

**C X-ray Findings** Radiologic evidence of demineralization may be present within days of onset, bony erosions and narrowing of the joint space followed by osteomyelitis and periostitis may be seen within 2 weeks.

### Differential Diagnosis

The septic course with chills and fever, the acute systemic reaction, the joint fluid findings, evidence of similar infection elsewhere in the body, and the dramatic response to appropriate antibiotics are diagnostic of pyogenic arthritis. Gout is excluded by the absence of hyperuricemia and other signs of gout. Acute rheumatic fever and rheumatoid arthritis commonly involve many joints and are not associated with chills. Pyogenic arthritis may be superimposed on other types of joint disease, notably rheumatoid arthritis.

### Treatment.

Prompt systemic treatment with penicillin or one of the broad-spectrum antibiotics (chosen on the basis of sensitivity studies) is usually effective. Local aspiration, irrigation with saline, intra-articular administration of antibiotics, and incision and drainage are sometimes indicated. Relieve pain with local hot compresses and by immobilization of the joint with a splint or traction (or both). Early active motion exercises within the limits of tolerance will hasten functional recovery.

### Prognosis.

With prompt antibiotic therapy (within 7-10 days of onset), functional recovery is usually complete. Bony ankylosis and articular destruction commonly occur if treatment is inadequate.

- Chartier, Y., Martin, W.J., & P.J. Kelly. Bacterial arthritis: experiences in the treatment of 77 patients. *Ann Int. Med.* 50: 1462-74, 1959.
- Ward, J., Cohen, A.S., & W. Bauer. The diagnosis and therapy of acute suppurative arthritis. *Arthritis & Rheumatism* 3: 522-35, 1960.
- Willkens, R.F., Healey, L.A., & J.L. Decker. Acute infectious arthritis in the aged and chronically ill. *Arch. Int. Med.* 106: 354-64, 1961.

## TUBERCULOUS ARTHRITIS

### Essentials of Diagnosis

- Chronic monoarthritis, only occasional involvement of a few peripheral joints.
- History or evidence of extra-articular tuberculosis is common.
- Systemic signs of disease are often minimal.
- Joint fluid findings or synovial biopsy are often diagnostic.

Differentiate from rheumatoid arthritis and arthritis due to other chronic infectious disorders such as the mycotic diseases.

### General Considerations

Tuberculous arthritis is almost always metastatic from a primary focus, often in the lungs or lymph nodes. It is most commonly seen in children. About one-half of patients give a history of trauma several weeks prior to the onset of joint symptoms. An early pathologic manifestation is the subchondral infiltration of tuberculous granulation tissue which undermines the articular cartilage and apparently absorbs the bony articular cortex. A diffuse synovitis with a pannus of granulation tissue may hasten the destruction of cartilage. In progressive disease the joint may be destroyed by massive caseation, and discharging sinuses may appear.

### Clinical Findings

**A Symptoms and Signs** Tuberculous arthritis of the peripheral joints is usually monoarticular, involving most commonly a knee or hip. The spine may also be involved. The onset is characteristically insidious, unattended by major systemic manifestations. Local discomfort causes a slight limp. Doughy swelling of the joint, mild local heat, muscle spasm and atrophy, and some limitation of

motion may be found. Large effusion is rare. Regional lymphadenopathy may indicate tuberculous adenitis.

**B. Laboratory Findings.** Tubercle bacilli are often demonstrable in the joint fluid by smear, culture, or guinea pig inoculation. Additional synovial fluid findings include polymorphonuclear leukocytosis with markedly reduced or absent sugar content. Biopsy of regional lymph nodes may reveal tuberculous adenitis; synovial biopsy is usually diagnostic. A positive tuberculin skin test is consistent with the diagnosis; a negative reaction makes the diagnosis unlikely.

**C. X-ray Findings.** Periarthritic demineralization and soft tissue swelling are the earliest x-ray abnormalities. Later signs may include marginal erosion, subchondral bone destruction, and narrowing or complete obliteration of the joint (cartilage) space. X-ray evidence of tuberculosis may be present in the chest or elsewhere.

#### Differential Diagnosis.

The slow, insidious appearance of monoarthritis in a patient who shows evidence of visceral tuberculosis justifies a presumptive diagnosis of tuberculous arthritis. The joint fluid findings and a synovial or regional lymph node biopsy will confirm the diagnosis and will differentiate tuberculous arthritis from other chronic arthritides such as rheumatoid arthritis.

#### Treatment.

In addition to antibiotics and chemotherapeutic agents, treatment should include immobilization, prolonged rest, and, when indicated, surgery. Orthopedic consultation is essential.

#### Prognosis.

The natural course is slowly progressive, with transient spontaneous remissions. Without treatment the disease may progress to articular destruction. Complete functional recovery may occur with early and proper treatment.

LaFond, E.M. An analysis of adult skeletal tuberculosis. *J. Bone & Joint Surg.* 40A:346-64, 1958.

## LESS COMMON JOINT DISEASES

### REITER'S SYNDROME

Reiter's syndrome is a clinical triad of unknown etiology, consisting of nonspecific urethritis, conjunctivitis, and arthritis, which occurs most commonly in young male adults. It may follow (within a few days to 4 weeks) sexual exposure or diarrhea, and is usually accompanied by a systemic reaction, including fever (without chills). The arthritis is most commonly symmetric and frequently involves the large weight-bearing joints (chiefly the knees and ankles). Additional clinical manifestations may include balanitis, ulcerations in the mouth, skin lesions indistinguishable from keratosis blennorrhagica, and carditis. While most signs of the disease disappear within days or weeks, the arthritis is apt to persist for several months or longer. Characteristically, the initial attack is self-limited and terminates spontaneously.

Recurrences involving any combination of the clinical manifestations are common and are sometimes followed by permanent sequelae, especially in the joints. X-ray signs of permanent or progressive joint disease may be seen in the sacroiliac as well as the peripheral joints.

Reiter's syndrome must be distinguished from gonococcal arthritis, postgonococcal rheumatoid arthritis, and rheumatoid arthritis or ankylosing spondylitis which incidentally follow nonspecific urethritis.

Treatment is symptomatic.

Weinberger, H.J., & others. Reiter's syndrome, clinical and pathologic observations, a long term study of 16 cases. *Medicine* 41:35-91, 1962.

### PALINDROMIC RHEUMATISM

Palindromic rheumatism is a disease of unknown etiology characterized by frequent recurring attacks (at irregular intervals) of acute arthritis. The attacks rapidly disappear in several hours to several days. The small joints of the fingers are most commonly affected, but any peripheral joint may be involved. Although hundreds of attacks may occur over

a period of years, there is no permanent articular damage. *Palindromic rheumatism must be distinguished from acute gouty arthritis and an atypical, acute onset of rheumatoid arthritis.*

Symptomatic treatment is usually all that is required during the attacks. *Chrysotherapy may be of value in preventing recurrences.*

### INTERMITTENT HYDRARTHROSIS

Intermittent hydrarthrosis is a rare clinical entity of unknown etiology which is characterized by recurring painless joint effusions, particularly in the knee, usually occurring at regular intervals and lasting several hours to several days. The existence of this entity has been questioned, and other causes of joint effusion must be carefully excluded before the diagnosis is considered.

Treatment is symptomatic.

### NEUROGENIC ARTHROPATHY

Neurogenic arthropathy is joint destruction resulting from loss or diminution of proprioception, pain, and temperature perception. Although usually associated with *tabes dorsalis*, it is also seen in diabetic neuropathy, syringomyelia, spinal cord injuries, subacute combined degeneration of pernicious anemia, and peripheral nerve injuries. With loss of the normal muscle tone and loss of protective reflexes, a marked traumatic osteoarthritis ensues, this results in an enlarged, painless joint with extensive erosion of cartilage and osteophyte formation.

Treatment is directed against the primary disease, mechanical devices are used to assist in weight-bearing and prevention of further trauma. In some instances, amputation becomes unavoidable.

## GENERAL PRINCIPLES IN THE PHYSICAL MANAGEMENT OF ARTHRITIC JOINTS

The following general principles apply to the treatment of any disease of the joints.

(1) Arrange or support the affected joints in comfortable positions which will permit optimal physical use if joint motion is subsequently lost.

(2) In the ankylosing forms of arthritis, after the acute process has subsided, employ active exercises or passive mobilization early and regularly, as tolerated, in order to prevent deformity and to preserve joint motion.

(3) Avoid measures which cause persistent increase in symptoms. So-called "routine measures," e.g. heat and massage, are not uniformly tolerated and there is no evidence that they improve function.

(4) Patients with joint disease (particularly rheumatoid or suppurative arthritis) are constantly threatened by deformity. Guard particularly against flexion deformities.

(5) The services of a specialist in physical therapy should be utilized whenever possible.

(6) If the arthritis is severe, if the course of the disease seems unfavorable, or if ankylosis appears inevitable, early consultation with an orthopedist is imperative. Special orthopedic measures such as traction, casts, braces and corsets, and surgical measures including arthroplasty, capsulotomy, tenotomy, arthrodesis and synovectomy may be required.

(7) Emphasize to the patient the importance of complete cooperation and his responsibility with the physical therapy program at home as well as in the office or hospital. Stress the importance of year-round continuance of treatment if necessary. Instruct the patient (or, if necessary, his family and friends) in the proper use of heat, immobilization and passive mobilization under home conditions.

## EXTRA-ARTICULAR DISORDERS

Certain extra-articular disorders cause musculoskeletal symptoms which may simulate joint disease. These include calcific tendinitis, shoulder-hand syndrome, fibrositis, and psychogenic rheumatism.

## CALCIFIC TENDINITIS (Bursitis)

Calcific tendinitis, the most frequent cause of acute pain in the shoulder is due to an inflammatory reaction around calcium deposits in or near one of the tendons of the rotator cuff (most frequently the supraspinatus). The exact mechanism of this process is obscure. The onset is frequently acute with pain so intense that the patient holds his arm close to his side in order to prevent movement. There is usually tenderness over the calcific deposit. On x-ray calcium deposits can usually be identified in the vicinity of the rotator cuff tendon.

Most cases respond promptly to injection of 1 ml of lidocaine (Xylocaine®) or 25-50 mg of hydrocortisone (or both) into the area of point tenderness. X-ray therapy or phenylbutazone (see acute gouty arthritis for dosage) also affords relief in many cases. Salicylates and physical therapy have a definite role in the restoration of function after the acute episode. In some instances, multiple areas of calcification or very large deposits may require surgical excision.

## SHOULDER-HAND SYNDROME

The shoulder-hand syndrome is probably due to a neurovascular reflex mechanism brought about by local or referred pain in a shoulder, with resultant swelling of the hand and wrist on the affected side. The shoulder pain may be secondary to local trauma or may be referred from a more remote area, as in myocardial infarction, osteoarthritis of the cervical spine, herpes zoster of a cervical nerve root, angina pectoris, pericarditis and cerebrovascular lesions. In 15-30% of cases no cause can be found. The diagnosis of the underlying disease usually focuses attention on the real nature of this lesion, although it may often be confused with rheumatoid arthritis, bursitis, and gout. The vasomotor disturbance and swelling in the hand may suggest scleroderma.

Treatment in addition to measures directed against the underlying disease consists of analgesics and physical therapy. Stellate ganglion block (with procaine) and systemic corticoids may be helpful but are rarely indicated if physical measures are applied promptly.

Steinbrocker O., & T G Argyros. The shoulder-hand syndrome. GP 21:101-10 April 1960.

## FIBROSITIS

Fibrositis is a disease of unknown etiology characterized by stiffness, aching and pain in nonarticular areas involving the muscles and their investing connective tissue sheaths. Although in some patients the onset may be related to acute infections, unusual physical activity, fatigue, or exposure to dampness, in most cases there is no significant history of a precipitating event. Young or middle-aged adults are most frequently affected and often appear to be in a state of emotional tension which makes it difficult in some instances to exclude psychogenic rheumatism. The onset is usually insidious, though it may be acute. The posterior shoulder girdle, interscapular area, neck, lower back, and trochanteric area of the thighs are the most frequently involved sites. Symptoms are most marked after periods of prolonged rest or following exposure to dampness or cold weather. Physical examination shows no demonstrable lesions and laboratory and x-ray studies are noncontributory.

Treatment is symptomatic and should include rest of the affected part, heat, massage, exercises, salicylates, and procaine injection of trigger points, if present.

## PSYCHOGENIC RHEUMATISM

Psychogenic rheumatism occurs most commonly in women between the ages of 40 and 70 and consists of various musculoskeletal complaints which do not fall into a recognizable pattern and are not relieved by analgesics, heat, and massage. It may be reported which have no conceivable anatomic basis and there are no objective findings despite severe symptoms. The physician can usually recognize in these patients a personality disturbance of sorts, although no specific personality pattern is characteristic.

Treatment is extremely difficult as the patient uses her illness as an attention-getting mechanism or as a shield from her environment and either consciously or subconsciously resists therapy. Salicylates and physical therapy may be employed during exploration of the underlying problems with the patient. Formal psychotherapy is of value, but is usually rejected by the patient.

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## Nervous System

Joseph G Chusid

### DISORDERS OF CONSCIOUSNESS

Disturbances of the sensorium may be associated with decreased motor activity (e.g., stupor or coma) or increased motor activity (e.g., excitement, delirium, mania). Sensorial disturbances may range from partial clouding to complete obliteration of consciousness. The pattern of reaction of these disorders depends upon the nature and intensity of the stimulus and the physical, mental, and emotional status of the patient. Causative factors include trauma, cerebrovascular accidents, drug and other poisonings, fever, metabolic disorders, meningitis, overwhelming infection, brain tumors, convulsive disorders, and cardiac decompensation.

#### STUPOR & COMA

Stupor ranges from partial to almost complete loss of consciousness. Coma is complete unconsciousness from which the patient cannot be aroused even by the most painful stimuli.

##### Etiology of Coma.

Coma may be of intracranial or extracranial origin. Examples are given below.

**A. Intracranial:** Head injuries, cerebrovascular accidents, CNS infections, tumors, convulsive disorders, degenerative diseases, increased intracranial pressure.

**B. Extracranial:** Vascular (shock or hypotension, as with severe hemorrhage, myocardial infarction, arterial hypertension), metabolic (diabetic acidosis, hypoglycemia, uremia, hepatic coma, Addisonian crisis, electrolyte imbalance), intoxications (alcohol, barbiturates, narcotics, bromides, analgesics,

ataractics, carbon monoxide, heavy metals) miscellaneous (hyperthermia, hypothermia, electric shock, anaphylaxis, severe systemic infections).

##### Clinical Findings

**A. History:** Interrogate the patient during lucid intervals. Valuable information may also be obtained from the patient's friends, relatives, and attendants. Inquire specifically about the patient's occupation, previous physical, mental, or emotional illness, trauma, the use of alcohol and drugs, epilepsy, and hypertension.

**B. Physical Examination:** Place particular emphasis on vital signs, evidence of injury or intoxication, and neurologic abnormalities. Do not assume that sensory disturbances are due to alcoholic intoxication merely because an alcoholic breath is detected. Inspect the head and body carefully for evidence of injury. Discoloration of the skin behind the ear often is associated with skull fractures (Battle's sign).

Observe respiration, which may be deep and labored (suggesting diabetic acidosis) or of the Cheyne-Stokes type. Puffing out of one cheek with each expiration indicates paralysis of that side of the face.

Spontaneous movements may indicate which areas are normal or may represent the onset of focal motor convulsions.

Paralysis of extremities may be determined by lifting each extremity and allowing it to fall. In light coma the paralyzed limb will fall heavily, whereas a normal limb will gradually sink to the bed. Vigorous stimulation of the feet may cause a normal leg to react, where a paralyzed leg will not. Passive motion may disclose diminished tone of affected limbs in acute or recent flaccid hemiplegia.

Decerebrate rigidity or the presence of tonic neck reflexes suggests dysfunction at a brain stem level.

Check the eyes carefully. Hemianopsia may be demonstrable in light coma by failure of flinching on threatening hand gestures initiated from the hemianopsic side. Pupillary differences may be of vital diagnostic impor-



tance; an enlarged pupil is often present with ipsilateral subdural hematoma. Papilledema indicates elevated intracranial pressure and is a grave prognostic sign.

Oculomotor paralysis of one eye is often associated with a ruptured aneurysm of the anterior portion of the circle of Willis.

Pronounced nuchal rigidity usually signifies meningeal irritation (meningitis, subarachnoid bleeding) or herniation of the cerebellar tonsils due to intracranial tumor or vascular accident.

**C. Laboratory Findings** Catheterize the patient if necessary and examine the urine especially for protein, blood, glucose, and acetone. Take hemoglobin, WBC, differential count, and hematocrit. Draw blood for NPN, glucose, and blood ammonia when indicated (for diagnosis of uremia, diabetic coma, or hepatic coma). Lumbar puncture should be considered for all comatose patients unless there are specific contraindications (e.g., suspected posterior fossa lesions). CSF examination and culture may be helpful. Special studies may be indicated, e.g., blood cultures and analysis of body fluids for evidence of toxins. Skull x-rays, EEG, cerebral angiography, and pneumography are valuable aids in brain tumor and subdural hematoma suspects. Order chest x-ray and other x-rays as indicated.

## Treatment.

**A. Emergency Measures** The immediate objective is to maintain life until a specific diagnosis has been made and appropriate treatment can be started.

1. Maintain adequate ventilation - First determine the cause of any respiratory difficulty (e.g., obstruction, pulmonary disease, depression of respiratory center, vascular collapse).

Keep airways open. Place the patient on his side or abdomen with his face to the side and his head well extended (never on his back or with the head flexed). If necessary, pull the tongue forward with fingers or forceps and maintain in an extended position (e.g., by pharyngeal airways). Aspirate mucus, blood, and saliva from the mouth and nose with a lubricated soft rubber catheter. If no suction apparatus is available, use a 25-50 ml. syringe. Endotracheal catheterization or tracheostomy may be necessary. (Caution: If the endotracheal tube remains in place for more than 2 hours, there is danger of laryngeal edema and further obstruction upon its removal.) The services of a trained anesthetist or otolaryngologist are desirable.

Artificial respiration may be administered if respirations have ceased or are failing (see p. 166). Closed cardiac massage (see p. 208) may be necessary.

Oxygen may be administered by mask, catheter, or tent as indicated (see p. 163).

2. Shock - Institute immediate treatment if patient is in shock or if shock is threatened (see p. 2).

**B. General Measures** The patient must be observed constantly. Place him in the "shock" position (unless contraindicated), and change body positions every 30-60 minutes to prevent hypostatic pneumonia and skin ulcerations. Catheterize the patient if coma persists for longer than 6-12 hours and the patient fails to void. If necessary, insert an indwelling catheter (with appropriate aseptic technique).

Provide proper fluid and nutrition with I.V. glucose, amino acids, and saline solutions for the first few days until the patient is able to take fluids by mouth. If the patient is comatose for more than 2-3 days, tube feedings should be employed.

Whenever possible, avoid sedation or other depressant medications until a specific diagnosis has been made. Sedation with paraldehyde or barbiturates may be necessary for mild restlessness in coma which is not due to barbiturate or other drug toxicity.

**I.V. urea:** Increased intracranial pressure (e.g., in brain tumor, head injury, brain swelling) may be reduced for 3-10 hours by I.V. administration of urea. Give urea as 30% sterile solution (in 10% invert sugar) in a dosage of about 1 Gm./Kg. at a rate of about 60 drops/minute. Poor renal function or active intracranial bleeding are contraindications.

**C. Specific Measures** Treat specific causes, such as fevers, infections, and poisonings.

Friedlander, W. J., Kiley, J. E., & A. O.

Schlip. The unconscious patient. Med. Sc. 11:301-14, 1962.

Hildebreth, E. A.: Care of the comatose patient. GP 17:117-25, 1958.

McNeely, D. E., & F. Plum: Brainstem dysfunction with supratentorial mass lesions. Arch. Neurol. 7:10-32, 1962.

## NARCOLEPSY

Narcolepsy is a chronic clinical syndrome of unknown etiology characterized by recurrent episodes of uncontrollable desire to sleep. It is frequently associated with a transient loss of muscle tone (cataplexy) especially during emotional reactions (laughing crying). The attacks of sleep may occur once or several times a day and may last minutes to hours. The sleep is similar to that of normal sleep but is apt to occur at inappropriate times such as during work or while walking or driving. Narcolepsy is about 4 times as frequent in males as in females.

## Treatment.

**A Amphetamine Sulfate (Benzedrine<sup>®</sup>)**  
The average dose is 10-20 mg t.i.d. but up to 175 mg daily may be required for some patients. The optimal dosage may be determined by starting with 10 mg each morning and increasing the dosage as necessary to control symptoms.

**B Dextro Amphetamine Sulfate (Dexedrine<sup>®</sup>)** Give 5 mg each morning initially and increase as necessary. Long-acting capsules (Dexedrine Spanules<sup>®</sup>) are available in 5, 10 and 15 mg doses.

**C Ephedrine Sulfate** Ephedrine is not as satisfactory as amphetamine but is helpful in many cases. The average dose is 25-50 mg ( $\frac{3}{8}$ - $\frac{3}{4}$  gr) 2-4 times daily.

**D Methylphenidate Hydrochloride (Ritalin<sup>®</sup>)** Used in doses of 5-10 mg 3-4 times daily (or more if necessary).

## Prognosis

Narcolepsy usually persists throughout life. Although the attacks of somnolence and sleep may be relieved by medical treatment the cataplexy and attacks of muscular weakness which accompany emotional reactions (laughing crying) are usually not affected by drug therapy.

Ganado, W. The narcolepsy syndrome. *Neurology* 8:487-96, 1958.

Yoss, R. E., & D. D. Daly. Narcolepsy. *Arch Int Med* 106:168-71, 1960.

## SYNCOPE &amp; VERTIGO\*

### VASODEPRESSOR SYNCOPE (Vasovagal Syncope, Simple Fainting, Benign Faint)

Vasodepressor syncope, the most common type, is usually characterized by a sudden fall in BP and a slowing of the heart. The causative stimuli may be sensory (e.g., sudden pain) or entirely emotional (e.g., grief or bereavement). The patient is usually upright when the faint occurs; recumbency rapidly restores consciousness. In the early phase there may be motor weakness, epigastric distress, perspiration, restlessness, yawning, and sighing respirations. The patient may appear anxious with a pale face and cold, moist extremities. After several minutes, lightheadedness, blurring of vision, and sudden loss of consciousness with decreased muscle tone may occur. If the patient remains erect a brief but mild convulsion may follow. Syncope is believed to occur when the arterial pressure drops below 70 mm Hg systolic and is usually precipitated by fear, anxiety, or pain. Electroencephalographic changes occur after the onset of unconsciousness.

The patient should be placed in the recumbent position with his head lower than the rest of his body. Inhalation of aromatic spirits of ammonia may be tried if necessary.

Karp, H. R., & others. Vasodepressor syncope: EEG and circulatory changes. *Arch Neurol* 5:94-101, 1961.

Wayne, H. H. Syncope: Physiological considerations and an analysis of the clinical characteristics in 570 patients. *Am J Med* 30:418-38, 1961.

### ORTHOSTATIC HYPOTENSION (Postural Hypotension)

Syncope may occur as the patient assumes an upright position. This type of syncope is characterized by repeated fainting attacks associated with a sudden drop in arterial BP when the patient stands up. Recognized contributory factors are prolonged convalescence and recumbency, idiopathic disorders of postural reflexes, sympathectomy, peripheral

venous stasis, chronic anxiety, and the use of antihypertensive drugs

Treatment is directed toward the underlying cause when possible. Withdraw or reduce the dosage of hypotensive drugs. Caution the patient against rising too rapidly from the sitting or lying position. If abdominal ptosis is present, an abdominal belt may help. Elastic stockings may be of value. Vasoconstrictor drugs may be tried but usually do not help.

## CAROTID SINUS SYNCOPE

Patients who suffer from attacks of carotid sinus syncope usually give a history of fainting associated with spells of dizziness between attacks. A definite relation between the attacks and sudden turning or raising of the head or the wearing of a tight collar may be elicited. The diagnosis is usually confirmed by reproducing an attack by firm pressure and massage over the carotid sinus for 10-20 seconds. **Caution:** Stimulate only one carotid sinus at a time. Care must be exercised in stimulating the sinuses in elderly patients. Cerebrovascular accidents have been precipitated by this maneuver.

Three types of carotid sinus syncope are known to occur. (1) The vagal type (most common) is most often seen in older persons. Carotid sinus pressure slows the heart rate. This response can be abolished by the injection of atropine sulfate, 1 mg ( $\frac{1}{160}$  gr.) I.V. (2) The vasomotor or depressor type occurs more frequently in younger individuals. Carotid sinus pressure causes a fall in BP which can be abolished by injection of 0.5 ml (8 min.) of epinephrine, 1:1000 solution, but is unaffected by atropine sulfate. (3) In the cerebral type carotid sinus pressure affects neither heart rate nor BP, and neither epinephrine nor atropine affects the reflex. A direct cerebral effect is postulated.

### Treatment.

Correct all abnormalities whenever possible. Eliminate emotional problems and forbid the use of tight collars. In severe cases, denervation of the sinuses may be necessary. Local anesthesia of the carotid sinuses abolishes all types of carotid sinus syncope.

**A Vagal Type.** Atropine sulfate, 0.4-0.6 mg ( $\frac{1}{150}$ - $\frac{1}{100}$  gr.) 3-4 times daily (or more, if needed), will usually abolish attacks. Ephedrine sulfate, 25 mg ( $\frac{3}{8}$  gr.) with phenobarbi-

tal, 15 mg. ( $\frac{1}{4}$  gr.) 3-4 times daily, or amphetamine sulfate, 5-10 mg ( $\frac{1}{12}$ - $\frac{1}{8}$  gr.), may be used.

**B. Vasomotor Type.** Ephedrine and phenobarbital as above will usually prevent attacks.

**C. Cerebral Type.** Drugs are of no value.

## SYNCOPE DUE TO CARDIOVASCULAR DISORDERS

Syncope due to cerebral anoxia resulting from a temporary fall in cardiac output may occur in Stokes-Adams syndrome, myocardial infarction, pulmonary embolism, and the onset of paroxysmal tachycardia, and occurs in certain other types of heart disease (e.g., aortic stenosis and tetralogy of Fallot). Syncope may occur with "cyanotic crisis" (low arterial oxygen saturation and low cardiac output).

Treatment consists of correcting the underlying abnormality.

## SYNCOPE DUE TO METABOLIC DISTURBANCES

In some types of syncope, impaired cerebral metabolism may be the most significant factor. These varieties include (1) anoxemia, as in patients with congenital heart disease, (2) severe chronic debilitating anemias, (3) hypoglycemia, as in labile diabetics after overexertion, or failure to eat after taking insulin, (4) acidosis, as in some patients with uncontrolled diabetes mellitus, (5) drug intoxication, as with barbiturates, (6) acute alcoholism, and (7) hyperventilation, with associated respiratory alkalosis and tetany.

Treat the specific cause whenever possible. Consciousness may be restored by rebreathing into a paper bag, breath-holding, or administration of  $\text{CO}_2$ , 5-10% with oxygen, by mask. Recurrent attacks of hyperventilation syndrome suggest that psychiatric consultation should be considered.

## SYNCOPE DUE TO IMPAIRED BRAIN CIRCULATION

Impairment of brain circulation may lead to syncope attacks. Syncope associated with transient focal neurologic findings is encountered among elderly patients with arteriosclerotic cerebrovascular disease. Dizziness followed by syncope can occur following abrupt head movements in patients with recent head injuries. Lightheadedness, and occasionally syncope, may occur in migraine in association with diminished cranial arterial blood flow. A type of syncope associated with hypersensitivity of the carotid sinus may occur with profound fall in BP and consequent impaired brain circulation. In some patients with brain tumors or vascular malformations, syncope episodes sometimes occur which may be related to displacement, engorgement, or insufficiency of cranial circulation.

## VERTIGO (Dizziness)

The terms "vertigo" and "dizziness" are generally used to denote the subjective sensation of rotatory movement, either of the individual or his environment, and implies an inability to orient the body in relation to surrounding objects. Vertigo is found mainly in disease processes involving the labyrinths, the vestibular portion of the eighth cranial nerve, and their nuclei or connections. True vertigo is usually manifested by nystagmus, falling to one side, and abnormal reaction to tests of vestibular function. Among the more common causes are Meniere's syndrome, acute labyrinthitis, organic brain damage involving the vestibular nerve, its end organs or connections, or the cerebellum, and drug and chemical toxicity.

Treatment is based upon accurate diagnosis of the underlying disorder.

## MOTION SICKNESS

Motion sickness is an acute illness characterized by anorexia, nausea, dizziness, and vomiting. The principal factors in its etiology are visual, kinesthetic, and psychologic. Physiologically, the vestibular apparatus appears to be involved.

## Prevention.

Preventive measures are often effective. Attacks of motion sickness are difficult to treat successfully.

A. The antihistamines appear to be of benefit. Dimenhydrinate (Dramamine®) or diphenhydramine hydrochloride (Benadryl®), 50-100 mg q i d, may be effective.

B. Meclizine hydrochloride (Bonine®), 50 mg. every 6-12 hours p. r. n., is a long-acting effective agent.

C. Cyclizine hydrochloride (Marezine®) is effective in oral or I M doses of 50 mg. every 4-6 hours p. r. n.

D. Parasympathetic depressants, alone or in combination with mild sedatives: scopolamine hydrobromide or atropine sulfate, 1-2 0.4 mg. (1/300-1/150 gr.) every 3-6 hours.

E. Mild Sedation. Phenobarbital, 15-30 mg. (1/4-1/2 gr.) every 3-6 hours, may help prevent attacks.

## HEADACHE\*

### HEADACHE DUE TO MENINGEAL INVOLVEMENT

This is the most severe type of headache. Salicylate analgesics are usually effective, but narcotics may be necessary if pain is severe. Lumbar puncture performed very cautiously sometimes relieves headache due to increased intracranial pressure (e.g., subarachnoid hemorrhage). It is of no value for relief of increased pressure in posterior fossa tumors.

Lumbar puncture headaches are believed to be due to leakage of CSF from the puncture site, and are more likely to occur when a large-bore needle is used. If headache is mild upon arising, acetylsalicylic acid may suffice. Intrathecal injection of small quantities of sterile normal saline may afford relief in severe cases.

Friedman, A. P., & others: Classification of headache. *Neurology* 12:378-80, 1962.  
Friedman, A. P., & H. H. Merritt: Treatment of headache. *J. A. M. A.* 163:111-7, 1957.

## MIGRAINE

Migraine is characterized by paroxysmal attacks of headache, preceded by psychologic or visual disturbances and sometimes followed by drowsiness. It is said to affect about 8% of the population. It is more frequent among women than men and occurs more commonly among persons with a background of inflexibility and shyness in childhood and with perfectionistic, rigid, resentful, and ambitious character traits in adult life. There is commonly a history of similar headaches in blood relations.

The headache of migraine is believed to result from vascular changes. An initial episode of cerebral, meningeal, and extracranial arterial vasoconstriction is believed to occur (accounting for the visual and other prodromal phenomena), followed by dilatation and distention of cranial vessels, especially of the external carotid artery. Increased amplitude of pulsation is said to determine the throbbing nature of the headache. Rigid, pipe-like vessels result from persistent dilatation, and the headache becomes a steady ache. A phase of muscle contraction, with pain, is believed to follow.

Migraine often begins in childhood, about half of migraine patients report their initial attack before the age of 15 years. Characteristically, the headache occurs in episodes associated with gastrointestinal or visual symptoms (nausea, vomiting, scintillating scotomas, photophobia, hemianopsia, blurred vision).

## Prevention.

Methysergide maleate (UML-491, Sansert®) may be effective in preventing vascular headache. The average daily dose is 4-8 mg., preferably 2 mg. with each meal. This drug is contraindicated in pregnancy, peripheral vascular disease, and arteriosclerosis.

## Treatment.

## A. Treatment of Acute Attack

1. Ergotamine tartrate (Gynergen®) 1.M. is the treatment of choice, 0.25-0.5 mg. ( $\frac{1}{240}$ - $\frac{1}{120}$  gr.) will relieve headache within an hour in most cases. Administer the drug as early in the attack as possible. Do not repeat more often than once weekly. Oral or sublingual administration is not generally advised because ergotamine is less effective by these routes and because of the possibility of overdosage, since if the patient vomits it is impossible to know how much of the drug he has absorbed.

The dosage is 4-5 mg. ( $\frac{1}{15}$ - $\frac{1}{12}$  gr.) sublingually or orally, continue with 2 mg. ( $\frac{1}{30}$  gr.) every hour until headache has disappeared or until a total of 11 mg. ( $\frac{1}{6}$  gr.) has been administered.

**Toxicity.** Do not administer ergotamine to patients in septic or infectious states or who have peripheral vascular or arteriosclerotic heart disease, or to pregnant women. A few patients complain of numbness and tingling of extremities and some muscle pains and tension.

2. Dihydroergotamine (D.H.E. 45®), in doses of 1 mg. ( $\frac{1}{60}$  gr.) I.M. or I.V., may be substituted for ergotamine tartrate. Repeat in one hour if necessary.

3. Ergotamine with caffeine (Cafergot®) or atropine is sometimes more effective by the oral route alone and requires a smaller total dose. It is available as suppositories for rectal use if vomiting prevents oral administration.

4. Pressure on the external carotid artery or one of its branches early in the attack may abolish pain. Oxygen, 100%, by nasal mask may relieve the acute attack.

**B. General Measures.** Until the drug begins to relieve headache, have the patient at rest in a chair. After headache has been relieved, he should rest in bed for at least 2 hours in a quiet, darkened room without food or drink. This will promote relaxation and is necessary to prevent another attack from occurring immediately.

**C. Aborting an Attack.** When the patient feels an attack of migraine coming on he should seek relaxation in a warm bath and then rest in bed in a quiet, darkened room. The following drugs may help: Pentobarbital, 0.1 Gm. ( $\frac{1}{2}$  gr.) orally, ergotamine tartrate (Gynergen®), 3-4 mg. ( $\frac{1}{20}$ - $\frac{1}{15}$  gr.) sublingually, or even acetylsalicylic acid, with or without codeine.

## HISTAMINIC (HORTON'S) CEPHALALGIA

"Histaminic cephalgia" is characterized by a sudden onset of severe unilateral pain. The pain is of short duration and subsides abruptly. Associated signs include redness of the eye, lacrimation, rhinorrhea or stuffiness of the nostril, swelling of the temporal vessels on the affected side, and dilatation of the vessels of the pain area. The headache involves the orbital area, frequently radiating to the temple, nose, upper jaw, and neck. Typical attacks

can be induced by injections of small quantities of histamine diphosphate. Attacks occur most frequently during sleep.

Diagnosis may be aided by a positive histamine test. 0.35 ml of concentrated solution of histamine diphosphate (2.75 mg/ml) injected subcut usually brings on a typical headache in 20-40 minutes in susceptible persons.

#### Treatment.

Subcut injection of 1 mg (1/60 gr) of histamine base (in histamine diphosphate solution) may reproduce the headache. Horton has therefore recommended "desensitization" to histamine, starting with histamine diphosphate, 0.25 ml b i d, and increasing each dose by 0.05 ml until a 1 ml dose is given. Thereafter, a maintenance dose of 1 ml 1-3 times weekly is injected.

### HEADACHES DUE TO MUSCULOSKELETAL INVOLVEMENT

Muscle contraction or spasm may be caused by disease of the muscle or adjacent structures or may be associated with excessive fatigue or emotional tension. The muscles attached to the occiput are most frequently involved and cause the characteristic "occipital headache." There may also be a feeling of pressure or tightness or a band-like constriction around the head associated with emotional tension.

Tension headaches are by far the most commonly encountered of all types. However, since emotionally disturbed patients may have headaches due to other causes, a complete and adequate history and examination is always necessary.

Tension headaches seem to have no precise localization and usually do not conform to the distribution of cranial or peripheral nerves or roots. The headache is described as being dull, drawing, pressing, burning, or vague in character, and is usually occipital and supra-orbital. Medications, including potent analgesics, may not give complete relief. Exacerbation of complaints and association with anxiety, worry, or other emotional upsets is not always obvious to the patient.

#### Treatment

Muscle spasm due to organic disease and bone or joint pain may be relieved by appropriate physical therapeutic measures. Analgesics are usually also of value. Specific

therapy should be directed at the underlying disease.

For muscle tension headache rest, relaxation, and freedom from emotional stress are of primary importance. Heat to the involved muscles by means of hot towels, a heating pad or a warm bath will help relieve the discomfort. Gentle massage of the muscles will usually also be of benefit. Drugs may be of value in acute cases, but prolonged use should be avoided. Phenobarbital, 15-30 mg (1/4-1/2 gr) q i d, will temporarily relieve many headaches due to "nervous tension." Acetylsalicylic acid or sedatives plus tranquilizers (see pp 502 and 503) may also be of benefit.

## CONVULSIVE DISORDERS (EPILEPSY)

#### Essentials of Diagnosis

- Abrupt onset of paroxysmal, transitory, recurrent alterations of brain function usually accompanied by alterations in consciousness.
- Signs may vary from behavioral abnormalities to continuous prolonged motor convulsions.
- Primary brain disorder may be present.
- Family history of epilepsy may be present.

Differentiate from other causes of loss of consciousness such as syncope following impaired blood supply to the brain and narcolepsy (no convulsions). Muscle spasms and contractions may also occur as part of a hysterical state but are not of a type which is seen in epilepsy.

#### General Considerations

Convulsive disorders are characterized by abrupt transient symptoms of a motor, sensory, psychic, or autonomic nature, frequently associated with changes in consciousness. These changes are believed to be secondary to sudden transient alterations in brain function associated with excessive rapid electric discharges in the gray matter. Seizures are more apt to occur in a patient with organic brain disease than in one with a normal CNS. Symptomatic epilepsy may be produced by a variety of pathologic states and intoxications (e.g., brain tumor, cerebrovascular accidents, head trauma, intracranial infections, uremia, hypoglycemia, hy-

pocalcemia, and overhydration). In idiopathic epilepsy, morphologic changes are not demonstrable. Individuals may inherit a convulsive tendency. The onset of idiopathic epilepsy is usually before the age of 30 years. Later age of onset suggests organic disease.

Some seizures tend to occur during sleep or following physical stimulation (e.g., light or sound). In some patients emotional disturbances play a significant "trigger" role.

### Clinical Findings.

#### A. Classification of Seizures

1. Grand mal (major epilepsy) - (Grand mal and petit mal may coexist.) A typical aura may herald a major seizure. It may be stereotyped for an individual, e.g., an "odd" sensation in the epigastrium, memory phenomena, or a particular unpleasant taste or smell. The aura may consist of a motor phenomenon (e.g., spasm of a limb, turning of the head and eyes) or a sensory aberration (e.g., numbness). The patient may remember or actually "see" a scene or event from his past.

Consciousness is apt to be lost soon after the appearance of the aura, the subject may fall to the floor and emit a cry. The skeletal muscles then undergo strong tonic contractions, dyspnea and cyanosis may be present. Severe generalized clonic convulsive movements of the body begin a few seconds later, usually becoming less frequent as the attack persists. Frothing at the mouth, loss of bladder and bowel control, tongue biting, bruises, and contusions commonly occur at this time. A period of flaccid coma follows during which the pupils may be dilated, corneal and deep reflexes absent, and the Babinski reflex positive. The patient may remain confused and disoriented during the initial stage of recovery. A period of deep sleep often follows. Upon awakening, the patient may complain of sore muscles.

2. Petit mal (minor epilepsy) - (Petit mal and grand mal may coexist.) The so-called "petit mal triad" includes myoclonic jerks, akinetic seizures, and brief absences (blank spells) without associated falling and body convulsions. A specific 3/sec. spike and wave EEG pattern is present.

Petit mal epilepsy is more often encountered in children. There may be momentary or transient loss of consciousness, so fleeting or hidden in ordinary activity that neither the patient nor his associates are aware of it. Classic petit mal is characterized by a sudden vacant expression, cessation of motor activity, and loss of muscle tone. Consciousness and mental and physical activity return abruptly. As many as 100 attacks may occur daily.

3. Jacksonian epilepsy - This type of epilepsy consists of a focal convulsion during which consciousness is often retained. The seizure may be motor, sensory, or autonomic in type. The seizure commonly starts in part of a limb (e.g., thumb or great toe) or face (e.g., at the angle of the mouth) as a localized clonic spasm, and spreads in a more or less orderly fashion. For example, a seizure may pass from the hand along the upper extremity to involve the shoulder, trunk, thigh, and leg muscles.

Loss of consciousness is apt to occur when the seizure spreads to the opposite side and becomes generalized.

The seizure may remain confined to the site of origin, waxing and waning in intensity ("epilepsia partialis continua").

4. Psychomotor seizures - In this category are included most types of attacks which do not conform to the classical criteria of grand mal, Jacksonian seizures, or petit mal. Automatism, patterned movements, apparently purposeful movements, incoherent speech, turning of head and eyes, smacking of the lips, twisting and writhing movements of the extremities, clouding of consciousness, and amnesia commonly occur. Temporal lobe foci (spikes, sharp waves or combinations of these) are frequently noted in the EEG, and striking accentuation of these abnormalities is often seen during light phases of sleep.

5. Status epilepticus - Recurrent severe seizures with short or no intervals between seizures are frequently of serious import. Patients who remain comatose are apt to become exhausted and hyperthermic, and may die.

6. Febrile convulsions - In the very young, convulsions may be associated with or precipitated by a febrile illness. A febrile convulsion is sometimes the initial convulsion of an epileptic child, and many of these children subsequently develop psychomotor seizures. Febrile convulsions are more common in children with a family history of epilepsy. Non-febrile convulsions often occur in patients with a history of febrile convulsions.

7. Massive spasms - This type of seizure is most commonly encountered in the first 2 years of life, especially in children with evidence of motor and mental retardation. Sudden strong contraction of most of the body musculature occurs, often resulting in transient doubling up of the body and flexion-adduction of the limbs. A characteristic EEG pattern ("hypsarrhythmia") is often present. A favorable response to treatment with corticotropin has been reported for some patients.

B. Laboratory Findings. EEG is the most important test in the study of epilepsy. In

## Drugs Used in Epilepsy

Drug	Indications	Average Daily Dose	Toxicity and Precautions	Remarks
Diphenylhydantoin sodium (Dilantin®)	Grand mal some cases of psychomotor epilepsy	0.4-0.6 Gm (6-9 gr) in divided doses	Gum hypertrophy (dental hygiene) nervousness rash ataxia drowsiness nystagmus (reduce dosage)	Safest for grand mal and psychomotor epilepsy May accentuate petit mal
Methylphenyl ethylhydantoin (Mesantoin®)	Grand mal some cases of psychomotor epilepsy Effective when grand mal and petit mal coexist	0.3-0.5 Gm in divided doses	Nervousness ataxia nystagmus (reduce dose) pancytopenia (frequent blood counts) exfoliative dermatitis (stop drug if severe skin eruption develops)	Does not cause gum hypertrophy
Trimethadione (Tridione®)	Drug of choice in petit mal	0.3-2 Gm in divided doses	Bone marrow depression pancytopenia exfoliative dermatitis (as above) photophobia (usually disappears dark glasses) nephrosis (frequent urinalysis discontinue if renal lesion develops)	Do not use alone for grand mal may aggravate this condition
Paramethadione (Paralidone®)	Petit mal	0.3-2 Gm in divided doses	As for trimethadione	Toxic reactions stated to be less than with trimethadione Other remarks as for trimethadione
Phenacemide (Phenurone®)	Psychomotor epilepsy	0.5-5 Gm in divided doses	Hepatitis (liver function tests at onset follow urinary urobilinogen at regular intervals) benign proteinuria (stop drug may continue if patient is having marked relief) dermatitis (stop drug) headache and personality changes (stop drug if severe)	
Phenobarbital	All epilepsies especially as adjunct	0.1-0.4 Gm (1 1/2-6 gr) in divided doses	Drowsiness (decrease dose) dermatitis (stop drug and resume later if dermatitis recurs stop drug entirely)	One of safest drugs May sometimes aggravate psychomotor seizures Toxic reactions rare
Mephobarbital (Mebaral®)	As phenobarbital	0.2-0.9 Gm (3-14 gr) in divided doses	As for phenobarbital	Usually has no advantage over phenobarbital and must be used in twice dosage
Bromides (potassium bromide or sodium bromide)	All epilepsies especially as adjuncts	3-6 Gm (45-90 gr) in divided doses	Psychoses mental dullness acneiform rash (stop drug may resume at lower dose)	Rarely used now Effective at times when all else fails
Metharbital (Gemonil®)	Grand mal	0.1-0.8 Gm in divided doses	Drowsiness (decrease dose)	Especially effective in seizures associated with organic brain damage and infantile myoclonic epilepsy
Primidone (Mysoline®)	Grand mal	0.5-2 Gm in divided doses	Drowsiness (decrease dose) ataxia (decrease dose or stop drug)	Useful in conjunction with other anticonvulsants
Phensuximide (Milontin®)	Petit mal	0.5-2.5 Gm in divided doses	Nausea ataxia dizziness (reduce dose or discontinue) hematuria (discontinue)	
Methsuximide (Celontin®)	Petit mal psychomotor epilepsy	1-2 Gm in divided doses	Ataxia drowsiness (decrease dose or discontinue)	



Drugs Used in Epilepsy (Cont'd.)

Drug	Indications	Average Daily Dose	Toxicity and Precautions	Remarks
Acetazolamide (Diamox®)	Grand mal.	1-3 Gm. in divided doses	in divided doses (0.25 Gm. t.i.d. initially). Drowsiness and paresthesias may occur. (Reduce dose.)	
Ethotoin (Peganone®)	Grand mal.	2-3 Gm. in divided doses	Dizziness, fatigue, skin rash (decrease dose or discontinue).	
Amino-glutethimide (Elipent®)	As phenobarbital.	0.75-1.5 Gm	Frequent skin rash.	Doriden® analogue. Usefulness not yet established.

some cases provocative measures (e.g., hyperventilation, sleep, drugs, photic stimulation) are of diagnostic value

Skull x-rays, CSF studies, blood glucose and blood calcium determinations, pneumograms, and cerebral angiograms may aid in determining the cause of convulsions

#### Differential Diagnosis.

In syncope there is an associated drop in BP, the muscles are flaccid, there are no convulsive movements initially, and the attack subsides with increased brain blood flow in recumbency.

In hysteria there is usually no loss of consciousness, incontinence, tongue biting, or self-injury. The patient may be resistive, and the "convulsion" is erratic and atypical

Narcolepsy is characterized by irreversible sleep attacks of brief duration, frequently associated with catalepsy (sudden loss of muscle tone, with no loss of consciousness precipitated by acute emotional disturbances such as fright or laughter)

#### Complications.

Fractures and soft tissue injuries may occur during seizures. Mental and emotional changes, particularly in poorly controlled epileptics, sometimes occur. Behavioral or emotional components may mask an underlying convulsive disorder. Examples are disorientation, hallucinations, excitement, incoherent speech, erratic behavior, automatisms, mental dullness, and irritability.

#### Treatment.

The objective of therapy is complete suppression of symptoms, though in many cases this is not possible. Most epileptics must continue to receive anticonvulsant therapy throughout life. However, if seizures are entirely controlled for 3-5 years, the dosage may be slowly reduced (over a period of 1-2

years) and finally withdrawn to ascertain if seizures will recur.

The patient must be acquainted with his disease and encouraged to become a member of local branches of groups interested in the welfare of epileptics, such as the American Epilepsy Society, the United Epilepsy Association, and the National Epilepsy League. Patients may receive information regarding research and treatment from these organizations

Excellent books about epilepsy are W.G. Lennox: *Science and Seizures*, Harper, 1941, T.J. Putnam: *On Convulsive Seizures, A Manual for Patients*, Lippincott, 1945, and F.A. Gibbs and F.W. Stamps: *Epilepsy Handbook*, Thomas, 1958

Epileptic patients should avoid hazardous occupations and driving. It is important to maintain a regular program of activity to keep the patient in optimal physical condition but avoiding excessive fatigue. Forbid all alcohol. Treat emotional factors as indicated. Impress upon the patient the absolute necessity of faithful adherence to the drug regimen. An epilepsy identification card should be carried at all times

Except in status epilepticus, no specific treatment is usually given during an attack except to protect the patient from injury. Anticonvulsant measures (see also p. 436) in the 4 principal types of epilepsy are as follows:

**A. Grand Mal: Caution:** Never withdraw anticonvulsant drugs suddenly

1. Diphenylhydantoin sodium (Dilantin®) is the drug of choice. Give 0.1 Gm. (1½ gr.) after the evening meal for 3-7 days, increasing dosage by 0.1 Gm. daily every week until seizures are brought under control. If attacks are severe and frequent, it may be necessary to begin with 0.3 Gm. (5 gr.) daily on the first visit. The average dose is 0.4-0.8 Gm. (6-9 gr.) daily. After convulsive seizures are controlled, the dosage may be reduced if desired,

but the dosage should immediately be raised again if symptoms return

2 Phenobarbital - If the patient is on maximum dosage of diphenylhydantoin and there is inadequate response, give phenobarbital in addition to diphenylhydantoin increasing dosage as with diphenylhydantoin, while maintaining full dosage of diphenylhydantoin. Some clinicians prefer to begin with phenobarbital and maintain without diphenylhydantoin if possible. In many cases the 2 drugs used in combination are more effective than either drug used alone.

3 Methylphenylethylhydantoin (Mesantoin®) If excessive gum hypertrophy results from the use of diphenylhydantoin, methylphenylethylhydantoin may be tried in its place. The dosage is the same. This drug may be effective where grand mal and petit mal coexist. Do not change suddenly to methylphenylethylhydantoin, but gradually substitute for diphenylhydantoin. Combinations of both may prove more useful than the individual drugs.

4 Bromides, primidone (Mysoline®), mephobarbital (Mebaral®) or ethosin (Pegamone®) may be tried (see p. 436).

B Petit Mal In very mild petit mal if attacks are rare, treat only with phenobarbital. Mild attacks can often be treated successfully with amphetamine sulfate (Benzedrine®), 5-10 mg 2-3 times daily. Do not use amphetamine if the patient also has grand mal, because this drug may precipitate grand mal attacks. Glutamic acid, 8-10 Gm daily, may decrease the number of attacks.

For moderate and severe petit mal, trimethadione (Tridione®), is the drug of choice. Unfortunately it is not an entirely safe drug since it causes bone marrow depression in some patients. Caution: Whenever this drug is used, perform CBC once or twice a week for the first month, then every 2 weeks for 2-3 months and monthly thereafter. Begin with 0.3 Gm. daily and increase the daily dose by 0.3 Gm. every 7 days until attacks are controlled. Do not give more than 2 Gm. daily.

If grand mal seizures occur also, trimethadione may aggravate this tendency. It may therefore be necessary to administer medication for grand mal seizures simultaneously, and in some cases to stop the trimethadione. Paramethadione (Paradione®) is said to be less toxic than trimethadione. It is almost equally effective in petit mal attacks, and may be effective where other drugs fail. Observe precautions as for trimethadione.

Phensuximide (Milontin®), phenobarbital, methsuximide (Celontin®), acetazolamide (Diamox®) or mephobarbital (Mebaral®) may prove useful (see p. 436).

C Status Epilepticus Amobarbital sodium (Amytal Sodium®), 0.5-1 Gm (7½-15 gr) I.V., may be given intravenously phenobarbital sodium, 0.4-0.8 Gm (6-12 gr), injected slowly may be used. Paraldehyde, 1-2 ml diluted in a triple volume of saline I.V. slowly is an effective alternative. If the convulsion continues, repeat the I.V. dose very slowly and cautiously, or give 8-12 ml 1.M. Diphenylhydantoin sodium (Dilantin Sodium®) may be injected I.V. at a rate not exceeding 50 mg (¾ gr) /minute. A total dosage of 150-250 mg (2½-4 gr) may be required. General anesthesia may be used if all measures fail. Diphenylhydantoin sodium (Dilantin Sodium®) 250-500 mg (4-7½ gr) I.M. daily or phenobarbital sodium 30-60 mg (½-2 gr) I.M. q 1 d (or both), may be required until the patient is able to take medication orally.

D Psychomotor Epilepsy Patients must be watched and guarded to prevent injury to themselves or others. Diphenylhydantoin sodium (Dilantin®), with or without phenobarbital as for grand mal epilepsy, is the treatment of choice. Phenacemide (Phenurone®) is also effective. Give initially 0.5 Gm t.i.d. and increase (until symptoms are controlled) up to 5 Gm daily in 3-5 equal doses. Methylphenylethylhydantoin (Mesantoin®), mephobarbital (Mebaral®), primidone (Mysoline®), acetazolamide (Diamox®), and methsuximide (Celontin®) alone or in combination with other drugs are frequently useful.

#### Prognosis

In epilepsy due to identifiable lesions, the outcome varies with the underlying disease. In idiopathic epilepsy, skillful use of anticonvulsant drugs causes significant improvement in the great majority of cases.

Crawley, J.W. The over-all management of the adult epileptic. *M. Clin. North America* 42:317-26, 1958.

DeJong, R.N. Psychomotor or temporal lobe epilepsy. *Neurology* 7:1-14, 1957.

Penfield, W., & others. Symposium on post-traumatic epilepsy. *Epilepsia* 2:109-43, 1961.

## CONGENITAL CNS DEFECTS

### SYRINGOMYELIA

#### Essentials of Diagnosis

- Loss of pain and temperature sense but preservation of other sensory function (painless burning or injury to hands)
- Weakness, hyporeflexia or areflexia, wasting of muscles at level of spinal cord involvement (usually upper limbs and hands)
- Hyperreflexia and spasticity at lower levels

Differentiate from other disorders involving the spinal cord such as tumors, platybasia, and cervical spine anomalies, from *tabes dorsalis* from amyotrophic lateral sclerosis (no sensory loss), and from multiple sclerosis (no diffuse involvement or pain-temperature dissociation)

#### General Considerations

Syringomyelia is a disease of the spinal cord and brain stem of unknown cause, associated with gliosis and cavitation of the spinal cord and brain stem. The onset of symptoms is usually in the third or fourth decade. Although the etiology is not known, a developmental defect has been inferred because other congenital defects are usually present also. A coincidence of syringomyelia and intramedullary tumors (gliomas, hemangiomas) has also been noted.

#### Clinical Findings

The characteristic clinical picture is that of muscular wasting and weakness, dissociation and loss of the pain-temperature sense, and signs of injury to the long tracts.

**A Symptoms and Signs** The most common form is cervical syringomyelia involving the cervical spinal cord. Loss of pain and temperature sensibility in the cervical and thoracic dermatomes in shawl-like distribution is characteristic. The following are variably present: Painless burns of the fingers or forearms; atrophy of the small muscles of the hands (usually present), weakness and atrophy of the shoulder girdle muscles, Horner's syndrome, nystagmus, vasomotor and trophic changes of the upper extremities, absence of deep reflexes of the upper extremities,

Charcot joints in affected limbs, spasticity and ataxia of the lower extremities, and neurogenic bladder.

Involvement of the lumbosacral spinal cord may also occur, with weakness and atrophy of the lower extremities and pelvic girdle, dissociated sensory loss in the lumbosacral area, bladder paralysis, and vasomotor and trophic disturbances of the lower extremities.

When the medulla oblongata of the brain stem is involved, the process may be referred to as syringobulbia. This is characterized by atrophy and fibrillation of the tongue, loss of pain and temperature sensibility in the face, and nystagmus. Dysphonia and respiratory stridor may occur.

**B Laboratory Findings** Myelography discloses the presence in many cases of partial or complete block in the zone of the syringomyelia. A characteristic deformity of the contrast column may be noted on the myelogram.

#### Differential Diagnosis

Spinal cord tumor gives a characteristic myelographic deformity, and is more apt to be associated with complete subarachnoid spinal block.

In multiple sclerosis the symptoms are intermittent and there are usually no associated trophic changes or scoliosis and no dissociation or loss of pain and temperature sensibility.

Amyotrophic lateral sclerosis is characterized by symmetric, widespread muscle wasting with no sensory loss, and fasciculations of muscle. In *tabes dorsalis* serology is positive, Argyll Robertson pupils may be present, and the areas of cutaneous sensory deficit are smaller.

Platybasia and cervical spine anomalies show characteristic skull and cervical spine x-rays and characteristic myelograms.

#### Treatment

The treatment varies with the degree of clinical involvement and evidence of block on myelography. Laminectomy and decompression may be required, with needle aspiration or myelotomy through the posterior median fissure of the spinal cord in properly selected cases. Roentgen therapy of the affected area of the spinal cord has also been recommended, but the effects are poor.

#### Prognosis

Syringomyelia is slowly progressive over a period of many years. Severe incapacity may occur because of paralysis, muscular

atrophies, and sensory defects in spinal cases, intercurrent infections, especially of the bladder, commonly occur. In syringomyelia death may occur in several months because of the destruction of vital medullary nuclei.

Netsky, M. Syringomyelia. A clinicopathologic study. Arch Neurol 70 741-77, 1953

## CERVICAL RIB SYNDROME

The brachial plexus and subclavian artery may be compressed in the neck by a rudimentary cervical rib, fibrous band, first thoracic rib, or tight scalene muscle giving rise to sensory, motor, or vascular symptoms in one or both upper extremities. The onset of symptoms has been related by some to the loss of tone in shoulder girdle muscles with age or excessive trauma to these parts incurred by lifting or straining.

### Clinical Findings

Cervical ribs rudimentary or fully developed are relatively common although frequently asymptomatic. Although they are often bilateral, cervical ribs may give rise to unilateral complaints. Prominence of the lower neck above the clavicle on one or both sides may be obvious on inspection. Pressure in this region will give rise to local pain as well as pain referred to the hand and arm. Pain and paresthesia particularly in the ulnar portion of the hand and forearm most commonly occur. Impaired perception of pain and light touch in the hand or forearm and muscular weakness of small hand muscles may also be present. Coldness and blueness of the hand and diminished pulsation in the radial and ulnar arteries may be noted. Horner's syndrome, resulting from damage to cervical sympathetics, has occurred. Adson's test or maneuver is usually positive on the affected side. The patient, seated with hands resting on thighs, takes a rapid deep inspiration, holds his breath, hyperextends his neck, and turns his head as far as possible first to one side and then the other. Obliteration of the pulse on one side is considered a positive test.

### Treatment & Prognosis

The clinical course is variable. Frequent remissions or slow progression occur. Temporary relief may be obtained by wearing a

slings support on the affected extremity. Rest in bed, traction on the neck, and the use of pillows to support the shoulders are also helpful. Surgical removal of cervical ribs, division of fibrous bands, or section of the scalenus anticus muscles may give permanent relief.

## VASCULAR DISEASES OF THE CNS

### CEREBROVASCULAR ACCIDENTS (Strokes)

#### Essentials of Diagnosis

- Sudden onset of neurologic complaints varying from focal motor or sensory deficits and speech defects to profound coma.
- May be associated with vomiting, convulsions, or headaches.
- Nuchal rigidity frequently found.

Differentiation from brain tumor, subdural hematoma, meningitis or encephalitis, hypertensive encephalopathy, multiple sclerosis, and other nervous disorders may be quite difficult. Cerebrovascular accident may cause an almost unlimited variety of neurologic symptoms, including hemiplegia, homonymous hemianopsia, monocular or binocular blindness, aphasia, hemihypesthesia, dizziness, quadriplegia, dysphagia, slurred speech, drowsiness, confusion, stupor, and coma.

#### General Considerations

Cerebrovascular accident or stroke is a focal neurologic disorder due to a pathologic process in a blood vessel. In most cases the onset is abrupt and evolution rapid, and symptoms reach a peak within seconds, minutes, or hours. Partial or complete recovery may occur over a period of hours to months.

Three basic processes account for most cerebrovascular accidents: thrombosis (about 60%), embolism (about 20%), and hemorrhage (about 20%). Other infrequent causes include recurrent ischemic attacks, hypertensive encephalopathy, migrainous hemiplegia, and syncope.

Cerebrovascular accident is uncommon in persons under 40 years of age. The most fre-

quent predisposing illnesses in cerebral thrombosis are cerebral arteriosclerosis, syphilis and other infections, dehydration, and trauma. Cerebral embolism may consist of small pieces of blood clot, tumor, or fat, or clumps of bacteria. Cerebral hemorrhage is usually caused by rupture of an arteriosclerotic cerebral vessel. Subarachnoid hemorrhage is usually due to rupture of a congenitally weak blood vessel or aneurysm.

Occlusion of a cerebral artery by thrombosis or embolism results in a cerebral infarction with its associated clinical effects. Other conditions may on occasion also produce cerebral infarction and thus may be confused with cerebral thrombosis or embolism. These include cerebral venous thrombosis, cerebral arteritis, systemic hypotension, reactions to cerebral angiography and transient cerebral ischemia.

Transient cerebral ischemia may also occur without producing a cerebral infarction. Premonitory recurrent focal cerebral ischemic attacks may occur and are apt to be in a repetitive pattern in a given case. Attacks may last for 10 seconds to one hour, but the average duration is 2-10 minutes. As many as several hundred such attacks may occur.

Narrowing of the extracranial arteries (particularly the internal carotid artery at its origin in the neck) by arteriosclerotic patches has been incriminated in some cases of transient cerebral ischemias and infarction.

### Clinical Findings

**A. Early Symptoms and Signs** Variable degrees and types occur. The onset may be violent, with the patient falling to the ground and lying inert like a person in deep sleep with flushed face, stertorous or Cheyne-Stokes respirations, full and slow pulse, and one arm and leg usually flaccid. Death may occur in a few hours or days. Lesser grades of stroke may consist of slight derangement of speech, thought, motion, sensation, or vision. Consciousness need not be altered. Symptoms may last seconds to minutes or longer, and may persist indefinitely. Some degree of recovery is invariable.

Premonitory symptoms may include headache, dizziness, drowsiness, and mental confusion. Focal premonitory symptoms are more likely to occur with thrombosis.

Generalized neurologic signs are most common with cerebral hemorrhage and include fever, headache, vomiting, convulsions, and coma. Nuchal rigidity is frequent with subarachnoid hemorrhage or intracerebral hemorrhage. Mental changes are commonly noted in the period following a stroke and may include

confusion, disorientation and memory defects. Specific focal signs and symptoms are apt to be associated with disorders of particular arteries.

**1 Middle cerebral artery** - Contralateral monoparesis or hemiparesis, numbness, tingling, dysphagia, homonymous hemianopsia, scintillating scotomas.

**2 Anterior cerebral artery** - Weakness or numbness of the opposite leg, reflex incontinence.

**3 Posterior cerebral artery** - Hemianopsia, scintillating scotomas, possibly blindness.

**4 Internal carotid artery** - Contralateral weakness, numbness, or dysphagia, transient blindness or amblyopia.

**5 Vertebral and basilar arteries** - Dizziness, monoparesis, hemiparesis, or quadriplegia, bilateral numbness, staggering gait, ataxia, diplopia, dysphagia, dysarthria, blindness, deafness, confusion, or loss of memory and consciousness.

**B Late Symptoms and Signs** Survivors of the acute phase of stroke often enter a convalescent or chronic recovery phase. Varied signs and symptoms may be present, usually resembling the acute manifestations and related to the location and degree of brain infarction or hemorrhage. Recovery is sometimes remarkably complete, so that altered brain function may be hardly demonstrable even with special tests (EEG, psychometrics, pneumoencephalography, etc.). Generally, however, patients have lesser degrees of their initial defects (e.g., hemiparesis, numbness, aphasia, hemianopsia, impaired mentation). Paralyzed limbs and parts in this later stage usually show signs of upper motor neuron disease: spastic weak muscles with little muscle atrophy, hyperactive deep reflexes, diminished or absent superficial reflexes, and pathologic reflexes such as a positive Babinski's sign.

**C Laboratory Findings** Careful lumbar puncture will reveal bloody CSF, often under increased pressure, in cerebral or subarachnoid hemorrhage.

**D X-ray Findings** Cerebral angiography is essential for the diagnosis of aneurysms and vascular malformations, and may show narrowing, occlusion, or other abnormality of extracranial as well as intracranial vessels. Skull x-rays may show a displaced pineal gland, or calcification within the vascular malformation or aneurysm.

**E. Special Studies** The EEG is abnormal in most major cerebrovascular accidents and may be used serially to help follow the clinical

### Diagnosis of Cerebrovascular Disorders\*

	Intracerebral Hemorrhage	Cerebral Thrombosis	Cerebral Embolism	Subarachnoid Hemorrhage	Vascular Malformation and Intracranial Bleeding
Onset	Generally during activity Severe headache (if patient is able to report findings)	Prodromal episode of dizziness aphasia etc of ten with improvement between attacks Unrelated to activity	Onset usually within seconds or minutes No headache Usually no prodrome Unrelated to activity	Sudden onset of severe headache unrelated to activity	Sudden stroke in young patient No headache Unrelated to activity
Course	Rapid hemiplegia and other phenomena over minutes to one hour	Gradual progression over minutes to hours Rapid improvement at times	Rapid improvement may occur	Variable apt to be at worst in initial few days after onset	Most critical period is usually in early stages
History and related disorders	Suspect diagnosis especially if other hemorrhagic manifestations are present and in acute leukemia aplastic anemia thrombopenic purpura and cirrhosis of the liver	Evidence of arteriosclerosis especially coronary peripheral vessels aorta Associated disorders diabetes mellitus xanthomatosis	Evidence of recent emboli (1) other organs (spleen kidneys lungs) extremities intestines (2) several regions of brain in different cerebrovascular areas	History of recent stiff neck headaches subarachnoid bleeding	History of repeated subarachnoid hemorrhages epilepsy
Sensorium	Rapid progression to coma	Relative preservation of consciousness	Relative preservation of consciousness	Relatively brief disturbance of consciousness	Relatively brief disturbance of consciousness
Neurologic exam	Focal neurologic signs or special arterial syndromes nuchal rigidity	Focal neurologic signs or special arterial syndromes	Focal neurologic signs or special arterial syndromes	Focal neurologic signs frequently absent nuchal rigidity positive Kernig and Brudzinski signs	Focal neurologic signs cranial bruit
Special findings	Hypertensive retinopathy cardiac hypertrophy and other evidences of hypertensive cerebrovascular disease may be present	Evidence of arteriosclerotic cardiovascular disease frequently present	Cardiac arrhythmias or infarction (source of emboli usually in the heart)	Subhyaloid (pre retinal) hemorrhages	Subhyaloid (pre retinal) hemorrhages and retinal angioma
BP	Arterial hypertension	Arterial hypertension frequent	Normotensive	Arterial hypertension frequent	Normotensive
CSF	Grossly bloody	Clear	Clear	Grossly bloody	Grossly bloody
Skull x ray	Shift of pineal to opposite side	Calcification of internal carotid artery siphon visible shift of pineal to opposite side may occur	Pineal apt to show little if any displacement	Partial calcification of walls of aneurysm sometimes noted	Characteristic calcifications in skull x rays may be present
Cerebral angiography	Hemorrhagic area seen as avascular zone surrounded by stretched and displaced arteries and veins	Arterial obstruction or narrowing of circle of Willis (internal carotid etc)	Arterial obstruction of circle of Willis branches (internal carotid etc)	Typical aneurysmal pattern in circle of Willis arteries (internal carotid middle cerebral anterior cerebral etc)	Characteristic pattern showing cerebral arteriovenous malformation

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course ECG may establish the presence of "silent" recent myocardial infarct, which is a contributing factor in certain cerebral infarctions

### Differential Diagnosis

In brain tumor there is a progression of clinical findings, elevated CSF pressure and protein, and papilledema. Focal neurologic signs are common.

Patients with subdural hematoma give a history of head trauma, and there is visible evidence of head injury, a shift of the pineal gland on skull x-ray, and a characteristic angiogram.

Meningitis and encephalitis are differentiated on the basis of CSF changes (clouding, increased cells, protein, pressure, positive culture).

Hypertensive encephalopathy is associated with elevated BP, and the episodes are frequently transient.

Multiple sclerosis shows diffuse neurologic findings, and the clinical course is characterized by remission and then progression.

### Treatment.

#### A. Acute Stage or Onset

1. General Measures - Place the patient at complete bed rest and handle him carefully to avoid injury. If he is agitated, give tranquilizers or sedatives as necessary. If he is unconscious or unable to swallow, do not attempt to give feedings by mouth. Maintain nutrition with tube feedings or by parenteral means. Catheterization may be necessary if spontaneous voiding does not occur.

2. Lumbar puncture - If hemorrhage has occurred, lumbar puncture may be performed very cautiously, removing just enough fluid to relieve severe headache. Caution: Do not attempt to elicit Queckenstedt's sign in patients with suspected hemorrhage.

3. Anticoagulant therapy - Maintenance on anticoagulant therapy (see p. 256) has been advocated for treatment and prevention of cerebral thrombosis or embolism and for thrombosis or insufficiency of the carotid or vertebral-basilar system. However, recent studies by several groups suggest that anticoagulant therapy helps only a few individuals in any large series of patients with the clinical picture of stroke. The evidence is most promising for transient cerebral ischemia. The risk of hemorrhage, particularly in hypertensive patients, is great.

Narrowing of the extracranial arteries (e.g., internal carotid) is now being evaluated and operative measures to correct the affected vessel are being studied.

#### B. Stage of Recovery and Convalescence

The rehabilitation of the patient with hemiplegia due to cerebral vascular accident should be started early and should be intensive. The details of the rehabilitation program are discussed in the Appendix.

### Prognosis

In cerebral thrombosis the outcome is determined to a great extent by the location and extent of the infarct as well as the general condition of the patient. The greater the delay in improvement, the poorer the prognosis.

In cerebral embolism, the underlying condition and the presence of emboli in other organs are significant factors.

In intracerebral hemorrhage the prognosis is poor, particularly in the presence of hypertension and arteriosclerosis. Intraventricular or brain stem hemorrhage is a discouraging sign.

If the patient survives the acute attack, the prognosis for life may be good. With active rehabilitation many patients are able to walk and care for themselves. Return of useful function to the upper extremity occurs less often. Patients can be trained to achieve some degree of recovery. The prognosis for functional recovery is poor in those patients with severe residual organic mental syndrome or sensory aphasia, and in those patients with profound, irreversible, or massive infarction or hemorrhage.

A classification and outline of cerebrovascular disease. *Neurology* 8:395-434, 1958.  
International Conference on Vascular Disease. *Neurology*, Vol. 11, No. 4, Part 2, 1961.  
Millikan, C.H. Diagnosis and management of cerebrovascular occlusive disease, *Mod Med* 30:148-75, 1962.

### INTRACRANIAL ANEURYSM (Subarachnoid Hemorrhage)

#### Essentials of Diagnosis

##### Before Rupture

- Headache on effort
- Disorder of cranial nerves II, III, and V
- Cranial bruit
- May be asymptomatic

##### After Rupture

- Sudden onset of severe headache without apparent cause
- Only brief disturbance of consciousness
- Nuchal rigidity
- Bloody CSF

Differentiate from intracranial tumor or other causes of sudden intracranial hemorrhage

#### General Considerations.

Intracranial aneurysms vary in size from 5-6 mm to 10 cm in diameter, and individual aneurysms may vary in size from time to time. Larger aneurysms may erode the bones of the skull and sella turcica and compress adjacent cerebral tissue and cranial nerves. Most are located near the basilar surface of the skull, and almost half arise from the internal carotid or middle cerebral arteries. They usually occur singly. A coincidence of congenital intracranial aneurysms and polycystic kidneys and coarctation of the aorta has been noted. Saccular aneurysms are rare in childhood, their peak incidence is between 35 and 65 years of age.

Fusiform dilatation of the basilar arteries or the terminal portions of the internal carotids may occur as a consequence of diffuse arteriosclerotic changes. Miliary, saccular aneurysms frequently occur near the bifurcation of a vessel in the circle of Willis and are associated with congenital abnormalities of the muscularis. A mycotic aneurysm, the result of an arteritis produced by bacterial emboli, is relatively infrequent. Larger aneurysms may be partially or completely clot-filled, occasionally they are calcified.

#### Clinical Findings

**A. Symptoms and Signs.** Prior to rupture, aneurysms may be asymptomatic or may cause symptoms depending upon their location and size. Headache on effort and symptoms of involvement of cranial nerves II, III, and V are apt to be present. A bruit is sometimes heard over the affected site.

Following rupture, the symptoms are those of acute subarachnoid hemorrhage. Recurrent unilateral headache which clinically resemble those of migraine sometimes occur. Convulsions due to cortical irritation by blood may occur. BP is often elevated.

**B. X-ray Findings.** By use of carotid or vertebral arterial angiography, an aneurysm may be demonstrated on x-ray.

#### Treatment & Prognosis.

In most cases the patient survives the first attack of hemorrhage, but recurrence of bleeding is likely. Because of the high mortality rate associated with spontaneous subarachnoid bleeding and the probability of recurrence of subarachnoid hemorrhage, intracranial aneurysms are considered a

serious pathologic entity. The choice of surgical as opposed to medical treatment rests upon many circumstances, including the size and location of the aneurysm, the clinical status of the patient, the skill and experience of the surgeon, and the current enthusiasm for a particular therapeutic regimen. Various surgical procedures, including "trapping" the aneurysm with clips on either side, clipping the neck of the sac, and packing muscle around the aneurysm, have been successful in some cases.

Crawford, T. Some observations on the pathogenesis and natural history of intracranial aneurysms. *J. Neurol. Neurosurg. & Psychiat.* 22:259-66, 1959.

Walker, A.E. Clinical localization of intracranial aneurysms and vascular anomalies. *Neurology* 6:79-90, 1956.

### CEREBRAL ANGIOMA

Subarachnoid hemorrhage from a cerebral angioma may bear a close clinical resemblance to a ruptured intracranial aneurysm. This type of angioma may vary from a few mm in diameter in the cortex to large masses of tortuous channels (arteriovenous shunt), and may be designated as capillary, venous, or arterial (although the vessels are all abnormal). Clinically, cerebral angiomas are often associated with seizures which usually start in youth and are focal in nature. The patient may be aware of a pulsating mass in the head, and a bruit may be audible. Roentgenograms may show crescentic linear calcifications in the vessel walls.

The prognosis for ruptured angioma is generally believed to be better than for rupture of an aneurysm of the circle of Willis, and depends upon the size and site of the lesion. Surgical removal, when feasible, is performed at most centers, however, since a severe neurologic deficit may follow surgery, particularly if the dominant cerebral hemisphere is involved, the choice of operative versus nonoperative treatment often presents the clinician with a therapeutic dilemma.

Patterson, J.H., & W. McKissock: A clinical survey of intracranial angiomas with special reference to their mode of progression and surgical treatment. *Brain* 79:233-66, 1956.



## BRAIN ABSCESS

### Essentials of Diagnosis.

- A history of preceding infection (e.g., otitis media, mastoiditis, bronchiectasis, septicemia) is often present.
- Progressive or focal neurologic features.
- Evidence of increased intracranial pressure may be present.

The clinical manifestations and the electroencephalographic, pneumographic, and cerebral angiographic findings in brain abscesses may be similar to those of other intracranial masses.

### General Considerations

Localized suppurations may occur within the brain as in other portions of the body. Following acute purulent infection, pus in brain tissue may be free or encapsulated. Abscesses vary in size from microscopic to an area covering most of a cerebral hemisphere.

Brain abscess is usually caused by staphylococci or pneumococci, although any of the common pyogenic bacteria may be found. The organism may gain access to the brain by direct extension from otitis media, mastoiditis, sinusitis, and infected head injuries, or, more rarely, via the blood stream from distant sources, such as lung infections and bacteremia.

Abscesses occurring by extension from infections of the middle ear or mastoid are usually located within the temporal lobe or cerebellum. Abscesses occurring by extension from the paranasal sinuses usually occur in the frontal lobe. Abscesses following bacteremia are apt to be multiple. Metastatic abscesses are commonly secondary to suppurative pulmonary infections.

### Clinical Findings.

**A. Symptoms and Signs.** A history or evidence of preceding infection is usually present. Otitis media, mastoiditis, sinusitis, bronchiectasis, or pneumonia is frequently present. Focalizing manifestations may occur, producing visual field defects, motor and other sensory changes, aphasia, and cranial nerve palsies similar to those caused by any other intracranial mass.

Signs of increased intracranial pressure may occur, such as papilledema, headache, and slowed pulse and respirations. Mild meningeal signs may be present, such as a mild rigidity of the neck and a positive Kernig sign. Somnolence and slowing of the mental processes are common. The temperature is mildly elevated and rarely exceeds 102° F. (39° C.) if complications such as meningitis do not occur.

**B. Laboratory Findings.** Air ventriculography, pneumoencephalography, or cerebral angiography is frequently necessary to determine the site of abscess.

**C. Special Examinations.** Brain abscesses may be located at operation with the use of needle aspiration.

### Differential Diagnosis

Brain abscesses may be confused with other clinical entities such as brain tumors, leptomeningitis, or encephalitis. In brain tumor, a history or evidence of preceding infection is usually absent and the CSF cell count is usually normal. Leptomeningitis can usually be differentiated by means of a positive culture of the CSF. Acute fulminating leptomeningitis is easily distinguished clinically from brain abscess, mild leptomeningitis, such as tuberculous and syphilitic leptomeningitis, may be clinically indistinguishable. Encephalitis usually fails to exhibit the focalizing signs of brain abscess and usually provokes more profound and severe changes in the sensorium and personality.

### Treatment & Prognosis.

Treatment consists of operative drainage of pus. Surgery is usually delayed until the abscess is firmly encapsulated. If the abscess is well encapsulated and if it is practicable to do so, excision in toto is sometimes performed. Marsupialization of the cavity, packing of the cavity, and various types of incision and drainage are commonly employed. After surgical drainage has been instituted, irrigations of the abscess cavity with antibiotic solutions are helpful. Treatment of the original focus of infection, such as a chronic mastoiditis, is sometimes necessary before a brain abscess will heal completely.

The use of chemotherapy has greatly improved the outlook for brain abscess. It has even been maintained that the formation of brain abscesses - e.g., in debilitated patients with pyogenic infections elsewhere - can be aborted with the use of appropriate antibiotic and sulfonamide drugs. Without treatment, brain abscess is usually fatal.

Loeser, E., & L. Scheinberg: Brain abscess, a review of ninety cases. *Neurology* 7: 601-9, 1957.

Spiri, M. P., Jr., & others: Observations on current therapy of abscess of the brain Arch. Neurol. 81:439-41, 1959

## TRAUMATIC DISEASES OF THE CNS

### HEAD INJURY

#### Emergency Evaluation.

Any patient who gives a history of head injury followed by unconsciousness, and any unconscious patient who may have sustained a head injury, should receive careful neurologic evaluation. Particular effort should be made to detect focal or progressive neurologic changes. Skull x-rays should be taken as soon as possible.

The following are the most important features of the examination

(1) State of consciousness - The depth and duration of unconsciousness usually reflect the degree of trauma. However, an initially alert and well-oriented patient may become drowsy, stuporous, and comatose as a result of progressive intracranial hemorrhage. During the first 24-48 hours it may be necessary to awaken the patient hourly to evaluate his degree of orientation, alertness, and general response to stimulation. Caution: Do not discharge this patient to home care unless it is certain that a responsible person will be on hand to awaken him from "sleep" every hour and to summon aid if he cannot be completely aroused.

(2) Vital signs - Temperature, pulse, respirations, and BP should be observed at intervals of one-half to 12 hours, depending upon the extent of injury.

(3) Paralysis - In the stuporous or unconscious patient, paralysis can be demonstrated only by careful examination. Loss of strength and motion, although of minimal grade, may indicate intracranial hemorrhage.

(4) Ocular signs - The pupils should be observed regularly along with the vital signs. A fixed dilated pupil often means an ipsilateral epidural or subdural hemorrhage or ipsilateral brain damage. Ophthalmoscopic examination may reveal evidence of papilledema (due to intracranial pressure) or retinal hemorrhage.

(5) Convulsions are apt to occur soon after a head injury, focal (Jacksonian) convul-

sions suggest an irritative lesion of the contralateral cerebral hemisphere. Cerebral contusion and laceration, often in association with epidural, subdural, or intracranial hemorrhage causes focal convulsions.

(6) Nuchal rigidity - Although nuchal rigidity may result from the subarachnoid bleeding often associated with head injuries, cervical spine injury must be ruled out by appropriate x-ray and clinical examinations.

(7) Bleeding from the ear - Otorrhagia suggests basilar fracture through the petrous pyramid of the temporal bone, but it may also occur as a result of traumatic rupture of the tympanic membrane or laceration of the mucous membranes without perforation of the drum.

#### General Considerations

Cranio-cerebral injuries are frequently classified on the basis of the nature of the injury to the skull, although the prognosis for recovery depends primarily upon the nature and severity of the damage to the brain.

Closed head injuries are those in which there is no injury to the skull or in which the skull injury is limited to simple undisplaced fracture of the skull. They may be considered clinically as mild, moderate, or severe. Mild head injuries are characterized by brief loss of consciousness (seconds to minutes) without demonstrable neurologic changes (usually the same as cerebral concussion). CSF findings are usually normal. Retrograde amnesia may be present. Moderate head injuries are characterized by longer periods of unconsciousness, frequently with abnormal neurologic signs, and are often associated with cerebral edema and contusion. Severe head injuries cause prolonged unconsciousness and abnormal neurologic signs and are usually associated with cerebral contusion and laceration.

Open head injuries include scalp lacerations, compound fractures of the skull, and various degrees of cerebral destruction. If fragmentation of bone occurs, there will be extensive associated contusion and laceration of the brain. Consciousness may not be impaired at first, although depression of consciousness may occur later if progressive intracranial bleeding or edema occurs. Scalp lacerations should be sutured immediately unless they overlie a depressed fracture or penetrating wound of the skull, in which case the skin wound is treated in conjunction with the fracture in the operating room.

Fractures may be simple or compound, and linear (with no displacement of fragments), comminuted, or depressed.

Cerebral edema ("wet brain") following head injury is believed to be due to brain swelling. Clinically, there is considerable variation in the severity of the findings. Localizing signs such as convulsions, hemiplegia, and aphasia are not uncommon. CSF pressure is usually slightly increased. At operation, the brain looks very pale and swollen.

Contusion or bruising of the brain at or directly contralateral to the zone of impact (contrecoup injury) may be limited to the superficial cortex, or associated hemorrhage into the underlying brain may also occur. Contusions frequently occur along the base of the posterior frontal lobes and the adjacent temporal lobe tips. Brain contusion is often clinically indistinguishable from concussion or laceration of the brain.

Brain laceration (a tear in the substance of the brain) usually occurs at the point of application of great force to the head or directly opposite (contrecoup effect). Lacerations involving the base of the brain usually cause death in a short time. Focal neurologic signs may persist after the acute episode has subsided. Associated subarachnoid or intracerebral hemorrhage is usually present, and the CSF is bloody. Brain laceration (or contusion) may occur with no injury (or minimal injury) to the skull. The frontal and temporal lobes are common sites. Minor injuries may cause tearing of the brain and meninges and extensive hemorrhagic necrosis of the cortex and subcortical white matter. Associated hemorrhage of the basal ganglia and brain stem may also occur. Laceration of arachnoid vessels may result in subarachnoid bleeding or the formation of subdural hematoma. Tearing of the middle meningeal artery or the dural sinuses or veins may be followed by bleeding into the extradural spaces.

### Clinical Findings

**A Symptoms and Signs** Transient loss of consciousness lasting seconds to minutes occurs classically with concussion of the brain. In coma which lasts for several hours or days there is a likelihood of edema or of contusion and laceration of the brain. The period of coma depends upon the extent and site of injury, in severe cases it may last for several hours, days, or weeks.

After the patient recovers consciousness, symptoms and signs are related to the severity and nature of associated brain injury. With mild concussion, the patient may be normal within a few minutes, with laceration or contusion of the brain, mental confusion is apt to be present. Hemiplegia, aphasia, cranial nerve paralysis, and other focal neurologic

signs may also be noted depending upon the nature and extent of the brain injury. The ipsilateral pupil is often dilated in dural hemorrhage.

In the recovery phase and for months thereafter there may be complaints of headache, dizziness, and personality changes ("post-traumatic cerebral syndrome").

Loss of memory for the period immediately after recovery of consciousness (post-traumatic amnesia) and for the period immediately preceding the injury (pretraumatic or retrograde amnesia) may occur and is often related to the extent of brain damage.

If the patient remains unconscious, diagnosis of a progressive intracranial hemorrhagic lesion is difficult. Vital signs (pulse rate, respirations, BP) may change, although these are not reliable in case of deepening or unusually prolonged coma. Exploratory trephination is indicated, cerebral angiography may show pathognomonic features of subdural, epidural, or intracerebral hemorrhage. Prolonged unconsciousness is believed to indicate severe damage to the brain stem, usually due to secondary hemorrhage or compression of the brain stem.

### B Laboratory Findings

1 Lumbar puncture is advisable to establish the presence of subarachnoid hemorrhage and to establish a baseline appearance and pressure of the CSF. CSF is frequently normal in all respects in brain concussion or cerebral edema. With contusion or laceration of the brain, bloody CSF under increased pressure may be found.

2 Skull x-rays should be taken as soon as the patient's physical condition permits. Cerebral angiography may help demonstrate subdural or intracerebral hematoma. A pneumogram often is useful in demonstrating ventricular distortion, shift, or dilatation following head injury.

3 EEG may be of diagnostic and prognostic aid in selected cases.

### Differential Diagnosis

The history of a blow to the head makes the etiology of the unconsciousness evident, however, especially where a history of trauma is lacking, it is necessary to differentiate head injury from other causes of unconsciousness such as diabetic, hepatic, or alcoholic coma, cerebrovascular accident, and epilepsy (where trauma to the head may actually occur during the attack).

Differentiate the neurologic findings following head injury from those caused by epidural hematoma, subdural hematoma, brain tumor, etc.

### Complications & Sequelae.

The complications of head injuries include vascular lesions (hemorrhage, thrombosis, aneurysm formation), infections (meningitis, abscess, osteomyelitis) rhinorrhea and otorrhea, pneumatocele, leptomeningeal cysts, cranial nerve injuries, and focal brain lesions. The sequelae include convulsive seizures, psychoses, mental disturbances, and the post-traumatic cerebral syndrome.

**A. Subarachnoid Hemorrhage** Bleeding into the subarachnoid space is often associated with other types of brain injury and is relatively common in traumatized patients who have been unconscious for one hour or more. The clinical and diagnostic features of traumatic and spontaneous subarachnoid hemorrhage are similar. Painful stiffness of the neck and the presence of fresh blood in the CSF are the usual findings.

**B. Subdural Hematomas.** Acute subdural hematoma may occur after a head injury in association with contusion or laceration of the brain. In such cases, especially when the subdural hematoma is not massive, the patient's clinical course may be unaffected by evacuation of the subdural hematoma. In chronic subdural hematomas, particularly when a history of head injury is not obtained, the clinical course may be variable or suggestive of an intracranial mass. In infants, the diagnosis may be readily established by direct needle aspiration of the subdural space at the lateral margin of the open anterior fontanelle (subdural tap). In others, the cerebral angiogram remains the single most reliable diagnostic test, since a highly specific angiographic pattern is usually found. However, changes suggestive of subdural hematoma may also be noted in skull x-ray (shift of pineal), pneumogram (shift and distortion of ventricle), and electroencephalogram (focal low amplitude or slow waves).

**C. Extradural Hemorrhage** Extradural hemorrhage classically follows traumatic rupture of the middle meningeal artery or vein, and may be difficult to detect early. A blow on the temporal area, with dazing or transient loss of consciousness and apparent quick return to normal, usually occurs. A "lucid interval," lasting as long as a day or more in extreme cases, customarily follows, during this time the patient develops signs of increased intracranial pressure. This is caused by the continued steady accumulation of blood in the extradural space from the bleeding middle meningeal vessel.

Trephining of the skull is frequently necessary to make the diagnosis. Blood may then be evacuated through the trephine openings.

A fracture which by x-ray is found to cross the middle meningeal groove should raise the suspicion that this syndrome may be present.

**D. Intracerebral Hemorrhage** A large subcortical hematoma may develop, but the most common findings are multiple small intracerebral hemorrhages near the contused area. The angiographic pattern is characteristic.

**E. Rhinorrhea and Otorrhea** Rhinorrhea (leakage of CSF from the nose) may follow fracture of the frontal bone with associated tearing of the dura mater and arachnoid. Erect posture, straining, and coughing usually cause an increase in the flow of fluid. Replacement of lost fluid by air entering the cranial vault through the same (or a similar) pathway may give rise to an aerocoele. Otorrhea (leakage of CSF from the ear) is usually of serious prognostic importance since it is caused by injuries to the more vital areas of the base of the brain.

Infection and meningitis are potential hazards in both instances and may be prevented by the early use of prophylactic antibiotic therapy. In the case of rhinorrhea, surgical repair of the dural tear may be necessary to stop the flow of CSF and to close off a potential route of infection.

**F. Cranial Nerve Paralysis** Injury to the cranial nerves may occur. Commonly affected nerves are the olfactory (anosmia), facial (paralysis), auditory (tinnitus and deafness), and optic (atrophy).

**G. Post-traumatic Syndrome** The post-traumatic syndrome is more common after serious head injuries, but severe symptoms may be produced by relatively minor injuries. Headache, giddiness, easy fatigability, memory defects, and impaired ability to concentrate are common complaints. Personality changes are not uncommon. Changes of posture, exposure to sunlight or heat, exercise, and alcohol ingestion are apt to make the symptoms worse.

On pathologic examination the brain may appear normal or may show severe cortical atrophy and ventricular dilatation.

**H. Post-traumatic Epilepsy** The exact incidence of seizures following head injuries is not known. In general, the more severe the

injury, the greater the possibility of seizures EEG studies are important in establishing the diagnosis

### 1 Other Complications of Head Injuries

1 Increased intracranial pressure may be manifested by changes in the level of consciousness, headache restlessness, unequal pupils a slowly falling respiratory rate a falling pulse rate a slowly rising BP, papilledema, hemiparesis, and elevated CSF pressure Intracranial bleeding (subdural epidural, or intracerebral) must be ruled out

2 Wound infection or osteomyelitis may be prevented by prophylactic antibiotic therapy in patients with compound or depressed fractures of the skull, rhinorrhea, otorrhea, or extensive scalp lacerations, and by meticulous aseptic technic for all dressings

3 Pulmonary infections or atelectasis may be prevented or treated by the proper use of suction, positioning on the side or if necessary, intubation or tracheostomy

4 Hyperthermia may result from injury to the hypothalamus or brain stem local or general infection or marked dehydration

5 Shock usually occurs in patients with head injuries complicated by other severe injuries to the trunk and extremities and must be treated at once (see p 2)

### Treatment

#### A Emergency Measures

1 Treat shock if present parenterally administered fluids and blood may be required (see p 2)

2 Maintenance of an adequate airway and pulmonary ventilation is vital The patient should be placed prone, with head turned to one side to facilitate drainage of secretions from mouth and to keep the tongue from obstructing the pharynx Endotracheal intubation or tracheostomy may be necessary to maintain an open airway Give oxygen if necessary (see p 163)

#### B General Measures

1 During the acute or initial phases, restlessness may be a disturbing factor Special nursing care and paraldehyde may be required Avoid morphine because of its medullary depressant effects Catheterization of a full bladder may ameliorate restlessness Lumbar puncture and removal of a small amount of bloody CSF may also relieve an agitated patient

2 Antibiotic treatment is always indicated if there is active bleeding or discharge from the nose or ears Give procaine penicillin G, 600 000 units b i d, or broad-spectrum

antibiotics, until the danger of infection is past

3 Continued careful observation is essential

### Course & Prognosis

Prognosis and course are related to the severity and site of cranial injury With simple concussion recovery is usually rapid With laceration of the brain, mortality may be 40-50%

Subdural or epidural hematoma ordinarily requires prompt surgical evacuation in order to prevent death or serious neurologic complications

In general, residual symptoms and signs in patients with head trauma are likely to be more extensive and incapacitating in those with the more severe types of brain injury It is not uncommon however for patients to remain symptomatic (headache dizziness impaired memory personality changes) even though neurologic diagnostic studies are negative

Predictions regarding the clinical outcome are more accurate when made 6-12 months after the injury or when the clinical status of the patient has stabilized Great variations occur in individual cases A patient in whom subdural hematoma has been successfully removed may recover completely On the other hand many patients continue to have severe complaints after an apparently trivial head injury A complicating factor in many cases is the role played by the "secondary gain" for the patient via lawsuits insurance and other types of compensation

Gurdjian, E S, & others Symposium on head injuries J Neurosurg 15 125-54, 1958

Ruge, D Neurological evaluation of the patient with craniocerebral injury Am J Surg 98 918-20, 1959

Schneider, R C The diagnosis and treatment of trauma to the central nervous system M Clin North America 40 1369-84, 1956

## HERNIATION OF INTERVERTEBRAL DISK

### Essentials of Diagnosis Lumbosacral Disk.

- Back pain aggravated by motion, and pain radiating down the back of the leg and aggravated by coughing or straining
- Weakness of muscles decreased sensation hyporeflexia of leg and foot
- Sciatic nerve painful to pressure and stretch (straight-leg raising)
- CSF protein may be elevated, myelograms reveal characteristic defect

### Essentials of Diagnosis Cervical Disk

- Paroxysmal pains and paresthesias from back of neck radiating into the arms and fingers, usually in distribution of C6, C7, or C8 accentuated by coughing sneezing straining
- Restricted mobility of neck cervical muscle spasm
- Paresthesias and pains in fingers, diminished biceps or triceps jerk weakness or atrophy of forearm and hand muscles
- Narrowing of vertebral interspace on x-ray, characteristic filling defect or deformity on myelogram

Differentiate the neurologic findings from those caused by spinal cord tumors, and the pain from that caused by arthritis and spinal column anomalies

### General Considerations

In most cases rupture or herniation of an intervertebral disk is caused by trauma. Sudden straining with the back in an "odd" position and lifting in the trunk-flexed posture are commonly recognized precipitating causes. The defect may occur immediately after an injury or following an interval of months to years.

The lumbosacral intervertebral disks (L5-S1 or L4-L5) are most commonly affected, producing the clinical picture of sciatica. Herniation occasionally occurs in the cervical region (characterized by cervical radicular complaints) rarely in the thoracic region.

### Clinical Findings

**A Symptoms and Signs** These usually depend upon the location and size of the herniated or extruded disk material. Compression of a nerve root by a disk may be confined to a single nerve root, however, several roots may be compressed (e.g., cauda equina by disk at L5-S1). Larger lesions may even compress

the spinal cord and produce symptoms commonly associated with tumors.

**1 Lumbosacral disk** - In the great majority (over 90%) rupture of the disk occurs at the level of the fourth or fifth lumbar interspace. This is characterized by straightening of the normal lumbar curve, scoliosis toward the side opposite the sciatic pain, limitation of motion of the lumbar spine, impaired straight-leg raising on the painful side, tenderness to palpation in the sciatic notch and along the course of the sciatic nerve, mild weakness of the foot or great toe extensors, impaired perception of pain and touch over the dorsum of the foot and leg (in L5 or S1 distribution) decreased or absent ankle jerk, and radiation of pain along the course of the sciatic nerve to the calf or ankle on coughing, sneezing, or straining.

**2 Cervical disk herniation** (5-10% of herniated disks) - The cervical disks most commonly involved are between C5-C6 and C6-C7. Paresthesias and pain occur in the upper extremities (hands, forearms, and arms) in the affected cervical root distribution (C6 or C7). Slight weakness and atrophy of the biceps or triceps may be present, with diminution of biceps or triceps jerk. The mobility of the neck is restricted with accentuation of radicular and neck pains by neck motion, coughing sneezing or straining. Long tract signs (extensor plantar response, sensory or motor impairment of lower levels, etc.) occasionally occur, indicating compression of the spinal cord by the disk.

**B Laboratory Findings** CSF protein may be elevated, and complete or partial CSF block is occasionally demonstrated.

**C X-ray Findings** Spine x-rays may show loss of normal curvature, scoliosis, and narrowing of the intervertebral disk. A characteristic roentgenologic defect in the subarachnoid space is usually produced by a herniated disk and is readily demonstrable by myelography. Electromyography (EMG) may be of value in localizing the site of a ruptured disk if characteristic denervation potentials can be demonstrated in muscles of a particular root distribution.

### Differential Diagnosis

In tumors of the spinal cord the course is progressive, CSF protein is elevated, partial or complete spinal subarachnoid block is present, and the myelographic pattern is distinctive.

In arthritis neurologic findings are usually minimal or absent, and the myelogram is usually negative.

Spinal column anomalies show characteristic x-ray findings, CSF findings are negative, and myelographic changes are dissimilar or absent

#### Treatment.

##### A. General Measures

1 Lumbosacral disk - In the acute phase, bed rest, heat applied locally to the back, salicylate analgesics, and the use of a bed board under the mattress are indicated. Traction to the lower extremities is frequently beneficial. The avoidance of severe physical effort and strain is essential to minimize recurrence of symptoms after the initial episode. Low back belts, braces, or supports may be beneficial. It is important to instruct the patient in the proper methods of bending, lifting (with knees flexed), and carrying (with the object held close to the body).

2 Cervical disk - In acute exacerbations of herniated cervical disks, bed rest with cervical halter traction is indicated. In subacute or mild episodes, intermittent cervical halter traction with various devices may be employed on an outpatient basis or at home. The use of a light collar may be helpful. Local application of heat, diathermy, and similar measures may be of temporary value.

B Surgical Measures If the response to conservative measures is poor or recurrences are disabling, discectomy is indicated.

#### Prognosis.

Conservative management with or without traction may bring about improvement to the point of "practical" recovery. Relief of pain usually follows removal of the damaged disk. Reversal of motor dysfunction, muscle atrophy, and skin sensory changes may occur.

Decker, H. G., & S. W. Shapiro. Herniated lumbar intervertebral disks. *Arch. Surg.* 75: 77-84, 1957.

Raaf, J. Some observations regarding 905 patients operated upon for protruded lumbar intervertebral disk. *Am. J. Surg.* 97: 388-99, 1959.

## INTRACRANIAL TUMORS

#### Essentials of Diagnosis

- Headache, personality changes, vomiting
- Focal neurologic changes, often progressive
- Increased CSF pressure, papilledema, evidence of space-occupying lesion demonstrable on special examination (EEG, angiogram, pneumogram)

Differentiate from other disorders which cause increased intracranial pressure or appear to be due to progressive cerebral lesions, e.g., intracranial abscess, arachnoiditis, aneurysm, subdural hematomas, and neurosyphilis, and from epilepsy and cerebrovascular accident.

#### General Considerations.

Intracranial tumors are believed to account for a greater percentage of admissions to the average neurologic service than any other disease of the nervous system with the exception of cerebrovascular and infectious diseases. Metastatic tumors to the brain arise principally from the lung, breast, gastrointestinal tract, and thyroid. Less frequently, sarcoma, hypernephroma, melanoblastoma, and retinal tumors are the primary sources.

Primary intracranial tumors are unlike the carcinomas and sarcomas found outside the brain in that they rarely metastasize outside the CNS. They may be of congenital origin, e.g., dermoids, teratomas, craniopharyngiomas, mesodermal origin, e.g., meningiomas, neurinomas, angiomas, and hemangioblastomas, pituitary origin, e.g., chromophobe tumors and chromophil tumors, or ectodermal origin, e.g., the gliomas.

Gliomas account for 40-50% of intracranial tumors in some series. Depending upon the principal cell types and morphology, gliomas are subclassified into various types (e.g., glioblastoma multiforme, astrocytoma, medulloblastoma, astroblastoma, ependymoma, oligodendroglioma). The majority of tumors of the brain in children arise from the cerebellum (medulloblastoma and astrocytoma). In adults, tumors of the cerebral hemispheres are common, particularly astrocytoma and glioblastoma multiforme. Gliomas of the brain in adults are most commonly encountered in the 40-50 year age group.

### Clinical Findings

**A. Symptoms and Signs** These are commonly divided into manifestations caused by the intracranial mass (headache, vomiting, papilledema) and those resulting from interference with local brain function. Focal neurologic changes frequently reflect the location of the tumor.

1. Frontal lobe tumor - These tend to produce a disturbed mental state with defective memory, impaired judgment, irritability, mood changes, and facetiousness. Convulsive seizures may occur, as well as loss of speech in left-sided (dominant hemisphere) tumor. Anosmia may occur with tumors at the base of the frontal lobe.

2. Parietal lobe tumor - Sensory and motor abnormalities are common. Motor or sensory focal seizures, contralateral hemiparesis, hyperreflexia, impaired sensory perception, astereognosis, and a positive Babinski toe sign may be present. With a left parietal lobe tumor aphasic components may be demonstrable.

3. Occipital lobe tumor - Visual alterations and seizures preceded by an aura of lights and visual hallucinations are characteristic. Contralateral homonymous hemianopsia frequently with sparing of the macular area often occurs. Headache and papilledema may be found.

4. Temporal lobe tumor - Convulsive seizures of the psychomotor type are commonly present, as is aphasia also if the dominant (left) cerebral hemisphere is involved. A contralateral homonymous visual field defect may be demonstrated.

5. Cerebellar tumor - This is characterized by disturbances of equilibrium and coordination, and early development of increased intracranial pressure and papilledema.

**B. X-ray Findings** Skull x-rays, lumbar puncture, pneumograms, electroencephalography, and angiography may aid in diagnosis and localization of an intracranial mass. Chest x-ray, gastrointestinal series, urograms, and other studies may be necessary to determine the primary site of a metastatic brain tumor.

### Treatment.

**A. General Measures** If V. urea 30% in 10% invert sugar, will reduce increased intracranial pressure for periods of a few hours and gives welcome relief in the operative and early postoperative phases of treatment. Symptomatic therapy, including the use of analgesics, anticonvulsants, and sedatives as required, is essentially the same as for patients with similar complaints not associated with brain tumors.

**B. Specific Measures** In general, treatment consists of surgical removal of the tumor, although gratifying results may be achieved in a small number of selected patients with intensive radiation. Pituitary tumors may be "cured" with x-ray treatment. Medulloblastoma of the cerebellum in children is highly sensitive to an initial course of irradiation, but recurrence is the rule. Radical excision and hemispherectomy is occasionally successful in selected cases.

### Prognosis

The outcome in any particular case depends upon the type, size, and location of the tumor. Early diagnosis and proper surgical treatment may be curative in benign tumors (meningiomas, neurinomas) as well as in certain gliomas (especially in frontal and occipital locations).

For the majority of patients with malignant brain tumors, the prognosis is poor.

- Heimburger, R. F., & others: Symposium on malignant intracranial neoplasms. *Am. J. Surg.* 93:911-59, 1957.  
Hetsky, M. G., & J. M. Watson: The natural history of intracranial neoplasms. *Ann. Int. Med.* 45:275-84, 1956.  
Odum, G. L., & others: Brain tumors in children. *Pediatrics* 18:856-70, 1956.

## DEGENERATIVE DISORDERS OF THE CNS

### MULTIPLE SCLEROSIS (Disseminated Sclerosis)

#### Essentials of Diagnosis

- Sudden, transient motor and sensory disturbances, impaired vision
- Diffuse neurologic signs, with remissions and exacerbations.
- Euphoria (late)
- Onset in early adult life
- Abnormal colloidal gold curve, increased gamma globulin in CSF.

Differentiate from other diseases of more or less generalized distribution such as neurosyphilis and postero-lateral sclerosis, and from those disorders causing multiple neurologic findings or affecting the brain stem.



or upper cervical cord such as posterior fossa tumors, platybasia, Arnold-Chiari malformation, and high spinal tumors

### General Considerations.

Multiple sclerosis is characterized by the onset in early adult life of progressive diffuse neurologic disturbances, with irregular fluctuating periods of exacerbation and apparent improvement or quiescence. The etiology is not known, a wide variety of degenerative, toxic, and inflammatory agents and deficiency states have been implicated in various theories of pathogenesis.

Irregular gray patches of degeneration occur in the brain and spinal cord with a predilection for the white matter, varying in size from a few mm to several cm.

### Clinical Findings.

**A. Symptoms and Signs** The initial attack and subsequent relapses may occur following acute infections, trauma, vaccination, serum injections, pregnancy, or types of somatic stress.

Signs of multiple involvement of the CNS may include slurred speech, intention tremor, nystagmus, retrobulbar neuritis, incontinence, spastic paralysis, pallor of the temporal halves of the optic disks, increased deep tendon reflexes, and bilateral extensor plantar responses. Late in the course of the disease the mental state is characterized by euphoria with little insight into condition or disability. Excited and even maniacal states may occur.

The illness, therefore, is characterized by the fact that (1) the neurologic lesions are widespread and cannot be explained on a single anatomic basis, and (2) the signs and symptoms are subject to repeated exacerbations and remissions.

**B. Laboratory Findings** The CSF may show a "first zone" or "second zone" colloidal gold curve. CSF gamma globulin is likely to be increased. No pathologic alterations in CSF may be noted in some patients.

### Differential Diagnosis.

Neurosyphilis is classically characterized by Argyll Robertson pupils and positive blood and CSF serology. Posterolateral sclerosis is usually associated with pernicious anemia and achylia, and signs of a posterior and lateral column disorder. Cerebral tumors cause progressive clinical findings, a distinctive EEG, characteristic pneumograms and cerebral angiograms, increased CSF pressure and protein, and a pineal shift in skull x-rays.

Friedreich's ataxia is manifested by scoliosis, club-foot, absent deep reflexes, and a positive family history. Platybasia, Arnold-Chiari malformation, and cervical spine malformation are differentiated on the basis of skull and cervical x-rays, partial subarachnoid spinal block, and positive myelograms. Tumors of the posterior fossa cause papilledema, increased CSF pressure, and characteristic ventriculograms and vertebral angiograms.

### Complications.

The hazards of chronic invalidism usually increase the longer the patient survives. The immediate cause of death is usually some intercurrent disease. Infections of the bladder and kidney are common.

### Treatment.

**A. Medical Treatment** There is no specific treatment. Steroids and vasodilators (inhalations of 5-10% CO<sub>2</sub>, histamine infusions, amyl nitrite inhalations) have been advocated for treatment of acute relapses, but the results are poor. Therapeutic claims have also been made for tolbutamide, isoniazid, vitamin B<sub>12</sub>, procaine, blood transfusions, and fast-fre diets, but their value has not been established.

**B. General Measures** Adequate sleep at night and rest in the afternoon have been found to make patients more comfortable. Avoid sudden changes in temperature (external or internal) to reduce vascular spastic phenomena (although the role of spasm has been questioned). Heat makes these patients much worse, cold often improves them temporarily.

Rehabilitation, physical therapy, and psychotherapy are indicated in an attempt to encourage the patient to live with his disability and make the most of whatever assets he still retains.

### Prognosis

The course is varied and unpredictable. In almost all cases there is a remission of the initial symptoms, but with each recurrence of a symptom the chances of remission decrease. Early remissions may be remarkably complete, later in the course of the disease remissions tend to be partial. Remissions may last several months to 2 years.

A clinical course of 10-20 years is not uncommon. In one large series, the average survival after onset of symptoms was estimated at 27 years.

Adams, R.D., & C. Kubik. The morbid anatomy of the demyelinating diseases. *Am. J. Med.* 12: 510-46, 1952.

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Symposium on disseminated sclerosis and  
allied conditions Proc Roy Soc Med 54  
1 42 1961

## PARALYSIS AGITANS (Parkinsonism)

### Essentials of Diagnosis

- Pill rolling tremor maximal at rest with fixed facial expression
- Slow shuffling often festinating gait
- Diminished motor power rigidity of limb muscles upon passive motion (lead pipe or cogwheel)
- Insidious onset in 50's and 60's with slow progression

Differentiate from other causes of tremor such as the finer more rapid senile tremor the early appearing and nonprogressive familial tremor the hysterical tremor associated with other functional symptoms and the tremor of hyperthyroidism or early CNS syphilis Distinguish the rigidity from the spasticity of pyramidal tract disease and the rigidity associated with arthritis and hysteria

### General Considerations

Paralysis agitans is characterized by involuntary tremors diminished motor power and rigidity the mental faculties are not affected Onset is usually in the 50's and 60's The disease definitely occurs as a complication of epidemic encephalitis and has been known to occur in vascular disorders neurosyphilis and following head trauma Reversible extra pyramidal reactions including paralysis agitans with gait and postural abnormalities rigidity tremor salivation and similar symptoms may follow the use of tranquilizers such as the phenothiazines In many cases however a precipitating cause is not known and these are attributed to degeneration of the cells and tracts of the striate bodies globus pallidus and substantia nigra

### Clinical Findings

The onset is insidious with increasing rigidity or tremor (or both) The rate of progression may be slow The facial expression may be fixed or less mobile than normal smiling spreads and disappears slowly The

body movements generally become slower There may be gradually increasing rigidity with diminished swaying of the arms in walking The legs may begin to feel stiff and heavy and excessive effort may be required to lift them from the ground in walking A stooping posture is common with the arms at the sides elbows slightly flexed and fingers abducted Intermittent tremor (about 2/sec) occurs which is worse when the limb is at rest Tremors frequently are of the pill rolling type involving the thumb index finger or wrist and are sometimes associated with a to and fro tremor of the head Emotional disturbances and fatigue are apt to aggravate the tremor

The limb muscles on passive motion are rigid (lead pipe or cogwheel) There may be difficulty in getting out of a chair so that several efforts or attempts to rise are made Turning is difficult even when standing or in bed Movements such as adjusting a tie buttoning the coat and brushing the hair ultimately become impossible without assistance Some patients have a tendency to break into a run or trot (festination gait) The voice tends to become weak low in volume and monotonous Oculogyric crises may occur

### Differential Diagnosis

**A Tremor** Senile tremor is finer and more rapid and not associated with muscular weakness or rigidity Hysterical tremor is inconstant increases when attention is called to the affected part and decreases when the attention is distracted Other hysterical symptoms are present also Familial tremor begins early in life is increased by voluntary motion and remains constant throughout life without other nervous abnormalities The tremors of hyperthyroidism toxic tremors (delirium tremens) and those seen in early general paralysis of syphilis are not difficult to distinguish from those of paralysis agitans

**B Rigidity** In catatonia a fixed rigid attitude is maintained for long periods and there are associated mental changes The spasticity which occurs in pyramidal tract disease affects selected muscles and is greatest at the beginning of passive motion and less as motion proceeds In multiple arthritis there is a history of pain and evidence of a joint and not a muscle disorder

### Treatment

**A Medical Measures** (See table on p 456) Treatment is mainly symptomatic A number of drugs have been found to be effective in alleviating the symptoms of parkinsonism These drugs are usually used in combi

nation to obtain the optimal therapeutic result. Combinations such as trihexyphenidyl (Artane®) and diphenhydramine (Benadryl®) t i d may be used initially. Caution Do not stop drugs abruptly when changing to new ones. The dosage of the new drug should be increased as the other drug is gradually withdrawn

**B, Surgical Measures** In carefully selected patients, surgical destruction of portions of the globus pallidus or the ventrolateral nucleus of the thalamus has proved highly beneficial

**C General Measures** Physical therapy should include massage, stretching of muscles, and active exercise when possible. The patient should be taught to exercise daily the muscles most severely affected, especially those of the hands, fingers, wrists, elbows, knees, and neck

Reassurance and psychological support are of decided value, stressing the positive aspects of the disease (1) symptomatic relief with drugs, (2) no impairment of mental faculties, (3) slow progression over many years, and (4) active research and the hope of therapeutic breakthroughs.

Avoid barbiturates. Permit moderate use of alcohol to relax tension. Nonbarbiturate sedatives (e.g., meprobamate, not phenothiazines) may be of value

### Prognosis.

The disease is usually slowly progressive, the patient may live for many years

With increased disability, patients are apt to become depressed, anxious, and emotionally disturbed

Treatment with drugs may produce temporary amelioration of complaints. In selected patients, operative treatment (pallidotomy, thalamotomy) may produce significant improvement of tremor and rigidity

Cooper, I.S.: Results of 1000 consecutive basal ganglia operations for Parkinsonism. *Ann. Int. Med.* 52:483-89, 1960.

England, A.C., Jr., & R.S. Schwab: The management of Parkinson's disease. *Arch. Int. Med.* 104:439-68, 1959.

### HEPATOLENTICULAR DEGENERATION (Wilson's Disease)

Wilson's disease is a familial disorder characterized by clinical findings of basal

ganglia disease and accompanied by cirrhosis of the liver and usually a greenish-brown corneal pigmentation (Kayser-Fleischer ring). A metabolic disturbance has been implicated because of the increased excretion of copper and amino acids in the urine and the decrease in caeruloplasmin of serum. The cerebellum, cerebral cortex, and other parts of the nervous system may also be affected. The onset of symptoms is insidious, usually between the ages of 11 and 25 years

Tremors and rigidity are the commonest early symptoms. Tremors are apt to be of the intention or alternating type, bizarre "wing-beating" of the upper extremities is accentuated by extension of these parts. The rigidity resembles paralysis agitans

Dimercaprol (BAL) has been reported to be effective in removing the excessive copper and presumably impeding the progress of the disease. The clinically useful dose is 2.5 mg / Kg 1 M b i d in courses of 10-12 days every other month. D, L-penicillamine is an effective chelating agent suitable for oral administration, and may far surpass the effect of BAL in increasing excretion of copper. Some of the specific manifestations may be palliated by symptomatic therapy

The course is progressive, with partial remissions and exacerbations until death occurs (usually within 10 years). The full effect of dimercaprol or penicillamine therapy on the course of longevity has not as yet been determined

Goldstein, N.P., & others: Treatment of Wilson's disease with D, L-penicillamine. *Neurology* 12:231-44, 1962.

Walshe, J.M.: Treatment of Wilson's disease with penicillamine. *Lancet* 1:188-92, 1960.

### CHRONIC PROGRESSIVE (HUNTINGTON'S) CHOREA

Huntington's chorea is a hereditary disease of the basal ganglia and cortex, characterized by the onset in adult life of choreiform movements and mental deterioration. Many cases in America have been traced to 2 brothers who emigrated to Long Island from England. The movements are abrupt and jerky, though less rapid and lightning-like than those of Sydenham's chorea. Any somatic musculature may be involved. The disease is chronically progressive and usually leads to death in about 15 years

## Antiparkinsonism Drugs

Drug	Chief Effect On				Dosage	Precautions and Remarks
	Tremor	Rigidity and Spasms	Akinetic (Weakness)	Oculogyric Crises		
Atropine sulfate 0.5% solution		X			3 drops t i d in a glass of water increasing by 1 drop every 3 days to 10 drops t i d or toxicity	May precipitate acute glaucoma in elderly persons and contraindicated in patients with glaucoma Blurred vision dryness of mouth vertigo and tachycardia are early toxic symptoms late symptoms are vomiting dizziness mental confusion and hallucinations The synthetic drugs are apt to cause more dizziness than the natural alkaloids and are somewhat less potent parasympatholytics
Belladonna tincture		X			15 drops t i d in a glass of water increasing by 1 drop every day to 30 drops t i d or toxicity	
Scopolamine hydrobromide	X			X	Elderly 0.3 mg (1/200 gr) b i d young up to 0.6 mg (1/100 gr) b i d or t i d	
Stramorium tincture	X				Start 15 drops t i d and increase slowly until a therapeutic response is obtained 60 drops t i d are being given or toxicity occurs	
Rabellon <sup>®</sup>		X	X		0.5 mg tablets 1/4-1/2 or 1 tablet 2-4 times daily	
Trihexyphenidyl HCl (Artane <sup>®</sup> )		X	X	X	1-5 mg t i d starting at low dosage and slowly increasing For oculogyric crisis use 10 mg t i d	
Biperiden HCl (Akineton <sup>®</sup> )		X		X	2 mg 3-4 times daily	
Procyclidine HCl (Kemadrin <sup>®</sup> )		X			2-5 mg t i d after meals	
Carbamiphen HCl (Panparmit <sup>®</sup> )		X			50-100 mg q i d Start with 12.5 mg q i d and gradually increase to optimal dosage	Administer on a full stomach or with 1 or more full glasses of water Other remarks as for atropine
Cycrimine (Pagitan <sup>®</sup> )		X	X	X	1-2.5 mg 3-4 times daily Dosage may be gradually increased up to the limits of tolerance	Useful when effects of trihexyphenidyl wear off Other remarks as for atropine
Benzotropine methane sulfonate (Cogentin <sup>®</sup> )	X	X			0.5 mg 1-2 times daily increasing by 0.5 mg at intervals of several days to 5 mg daily or toxicity Often most effective as single dose at bedtime	Side effects similar to atropine Best effect by combining with trihexyphenidyl or dextro amphetamine
Diphenhydramine HCl (Benadryl <sup>®</sup> )	X				50 mg 2-4 times daily	Reduce dosage if transient drowsiness occurs
Orphenadrine HCl (Disipal <sup>®</sup> )	X	X			50 mg 3-5 times daily	
Chlorphenoxamine ether HCl (Phenoxene <sup>®</sup> )		X			50 mg 3-4 times daily	Valuable adjunct to other drugs
Ethopropazine HCl (Parsidol <sup>®</sup> Lysothane <sup>®</sup> )	X	X			25-30 mg q i d	May be used in conjunction with other antispasmodic drugs Drug is related to chlorpromazine precautions as for this class of drugs
Dextro amphetamine sulfate (Dexedrine <sup>®</sup> )			X		5 mg morning or noon	CNS stimulant to be used with caution in cardiac patients

\*Rabellon<sup>®</sup> is a mixture of hyoscine atropine and scopolamine

Treatment is symptomatic. Large doses of tranquilizers, such as reserpine or one of the phenothiazines, are helpful in management.

Symposium on Huntington's chorea. Proc. Staff Meet, Mayo Clin 30 349-70, 1955.

## POSTEROLATERAL SCLEROSIS (Combined System Disease)

### Essentials of Diagnosis

- Numbness, "pins and needles," tenderness, weakness, feeling of heaviness of toes, feet, fingers, and hands
- Stocking and glove distribution of sensory loss, extensor plantar response, hyperreflexia, flexor spasms, flaccid paralysis and hyporeflexia less often, loss of position and vibratory sense
- Memory defects or psychotic states
- Associated blood and gastric findings of pernicious anemia

The presence of macrocytic anemia and achlorhydria usually makes the diagnosis more certain, but it may be necessary to distinguish from the familial ataxias, tabes dorsalis, multiple sclerosis, myelitis, and spinal compression by tumor.

### General Considerations.

Posterolateral sclerosis is a progressive degeneration of the posterior and lateral columns of the spinal cord, sometimes with degeneration of the peripheral nerves. The middle and older age groups are most often affected.

Although posterolateral sclerosis is usually associated with pernicious anemia, its severity does not necessarily parallel the degree of anemia, which suggests that the causes of spinal cord and blood changes may not be the same. Degeneration of the spinal cord may develop before clinical manifestations of pernicious anemia.

### Clinical Findings.

Tingling, numbness, and "pins and needles" sensations in the toes and feet and later in the fingers are the first symptoms. Sensations of swelling, coldness, and wetness of the feet may occur. Weakness of the legs, fatigue, a feeling of heaviness in the feet, and unsteady gait are common. Dyspnea on exertion with recurrent episodes of dizziness may be produced by the anemia, gastric distress may result from achlorhydria.

In the flaccid type the involvement is principally of the peripheral nerves, manifested as follows: Weakness of the lower extremities (especially of the distal segments), tenderness of the soles and calf muscles, stocking distribution impairment of touch sensibility in the lower extremities up to knee level, loss of appreciation of vibratory sensation, ataxia, a positive Romberg sign, depression or absence of knee and ankle jerks, and extensor plantar responses. In the spastic type spinal cord signs, especially of the lateral columns, predominate. Increased deep tendon reflexes, clonus and hypertonicity of muscles, and flexor spasms with progressive weakness. Paraplegia in flexion may follow. When sensory losses become more severe, loss of sphincter control and decubiti may occur.

Mental symptoms may also be present, even early in the disease. Apathy, mental dullness, hypomania, paranoid states, hallucinations, disorientation, and memory defects have been reported.

Laboratory findings are as for pernicious anemia (see p. 265).

### Treatment.

Treat as for pernicious anemia (see p. 266).

### Prognosis

With adequate treatment of pernicious anemia, improvement, especially of peripheral nerve involvement, may occur. Little improvement can be expected when the spinal cord is severely affected.

Paresthesias and sensory changes may persist even in those treated intensively, early, and fully.

The prognosis is worse in patients over 60 years of age.

See references under Multiple Sclerosis, p. 453.

## DISORDERS OF CRANIAL NERVES

### TRIGEMINAL (TRIFACIAL) NEURALGIA (Tic Douloureux)

Trigeminal neuralgia is characterized by a sudden attack of excruciating pain of short duration along the distribution of the fifth cranial nerve. The attack is normally precipitated by stimulation (usually mild) of a "trigger zone" in the area of the pain, and is char-

acterized by recurrent paroxysms of sharp, stabbing pains in the distribution of one or more branches of the nerve. The onset is usually in middle or late life, and the incidence is higher in women. The pain may be described as searing or burning, occurring in lightning-like jabs, lasting only 1-2 minutes or as long as 15 minutes. The frequency of attacks varies from many times daily to several times a month or a year. The patient often tries to immobilize his face during conversation, or attempts to swallow food without chewing in order not to irritate the trigger zone.

#### Treatment.

A. Medical Treatment. Medical treatment is generally unsatisfactory, but the following usually are tried before resorting to surgery.

1. Trichloroethylene (Trilene<sup>®</sup>), 15-20 drops a day by inhalation from a handkerchief, in a single dose or in divided doses one-half hour before meals.

2. Massive doses of vitamin B<sub>12</sub> (1 mg i M daily for 10 days) have been reported to relieve the severe pain.

3. Stilbamidine isethionate has been shown to produce a chemical neuropathy affecting the facial and cervical skin areas. Give a series of 10 daily I V injections of 0.15 Gm freshly dissolved in 150 ml of 5% glucose in distilled water over a period of one-half hour. Relief of pain may be delayed 1-5 months until the chemical neuropathy occurs. In a small percentage of cases treated with stilbamidine, unpredictable and troublesome formication and paresthesias of the face occur.

4. Anticonvulsants, e.g., diphenylhydantoin sodium (Dilantin<sup>®</sup>), 0.1 Gm (1 1/2 gr) q i d, or vasodilators, e.g., tolazoline hydrochloride (Priscoline<sup>®</sup>) 50 mg q i d, have been reported to be beneficial in some cases.

5. Alcohol injection of the ganglion or the branches of the trigeminal nerve may produce analgesia and relief from pain for several months or years. Repeated injections may be required at later intervals.

B. Surgery may be required if medical treatment gives no relief.

#### Prognosis

In most cases the paroxysms of pain are present for several weeks or months. Remissions may last from a few days to as long as several months or years. As patients become older, remissions tend to become shorter.

Iannone, A., Baker, A.B., & F. Morrell:  
Dilantin in the treatment of trigeminal neuralgia. *Neurology* 8:126-8, 1958.

List, C.F.: Pathogenesis of trigeminal neuralgia. *Arch. Neurol.* 77:36-43, 1957.

### BELL'S PALSY (Peripheral Facial Paralysis)

Bell's palsy is a paralysis of all the muscles of one side of the face, usually precipitated by exposure, chill, or trauma. It may occur at any age, but is slightly more common in the age group from 20 to 50.

Assure the patient that recovery usually occurs in 2-8 weeks (or up to 1-2 years in older patients). Keep the face warm and avoid further exposure, especially to wind and dust. Protect the eye with a patch if necessary. Support the face with tape or wire anchored at the angle of the mouth and looped about the ear. Electric stimulation (every other day after the 14th day) may be used to help prevent muscle atrophy. Gentle upward massage of the involved muscles for 5-10 minutes 2-3 times daily may help to maintain muscle tone. Heat from an infra-red lamp may hasten recovery.

In the vast majority of cases partial or complete recovery occurs. When recovery is partial, contractures may develop on the paralyzed side. Recurrence on the same or the opposite side is occasionally reported.

Jongkees, L.B.W. Treatment of Bell's palsy. *Neurology* 7:697-702, 1957.

Lathrop, F.D. Affections of the facial nerve. *J. A. M. A.* 152:19-26, 1953.

## DISORDERS OF PERIPHERAL NERVES

### POLYNEURITIS (Multiple Neuritis, Peripheral Neuropathy)

#### Essentials of Diagnosis

- Slowly progressive muscular weakness, paresthesias, tenderness, and pain, mostly of distal portions of extremities.
- Stocking and glove hypesthesia or anesthesia, especially for vibratory sense.
- Hyporeflexia or areflexia.
- Muscular wasting of affected parts.

Differentiate from neuritis involving only a single nerve and its distribution.

tabes dorsalis, which is not associated with muscular atrophy or nerve tenderness, acute anterior poliomyelitis with systemic as well as neurologic manifestations, and myositis, in which there is no nerve involvement and usually no sensory or reflex changes

#### General Considerations

Polynuropathy is a syndrome characterized by widespread sensory and motor disturbances of peripheral nerves. It may appear at any age, although it is most common in young or middle-aged adults, especially in men. In most cases a noninflammatory degeneration of the peripheral nerves is present.

Polynuropathy may be caused by (1) chronic intoxications (e.g., alcohol, carbon disulfide, benzene, phosphorus, sulfonamides), (2) infections (e.g., meningitis, diphtheria, syphilis, tuberculosis, pneumonia, Guillain-Barré syndrome, mumps), (3) metabolic causes (e.g., diabetes mellitus, gout, pregnancy, rheumatism, porphyria, periarthritis nodosa, lupus erythematosus), and (4) nutritional causes (e.g., beriberi, vitamin deficiencies, cachectic states).

#### Clinical Findings.

Symptoms usually develop slowly over a period of weeks. Notable exceptions with rapid onset may occur in infections plus alcoholic polynuropathy. Pains, tenderness, paresthesias, weakness and fatigability, and sensory impairment may be present. The pains may be mild or, occasionally, burning and sharp. Muscular weakness is usually greatest in the distal portions of the extremities. Impaired sensory perception, especially of vibration, is frequent, in alcoholic and arsenical polynuropathy, severe and extensive sensory defects may occur. The cutaneous sensory defect may consist of hypesthesia or anesthesia in an irregular stocking or glove distribution.

Tendon reflexes are usually depressed or absent. With paralyzed toes, the plantar response may be absent, with weak abdominal muscles, abdominal skin reflexes may be diminished or absent. Flaccid weakness and muscular atrophy of affected parts may occur, especially in the distal portions of the extremities. Foot drop with associated steppage gait may result.

Trophic changes of the skin of the extremities are manifested by a glossy red skin and impairment of the sweating mechanism. Muscles and nerves may be tender and hypersensitive to pressure and palpation.

#### Treatment.

**A. Specific Measures.** Remove from exposure to toxic agents (e.g., alcohol, lead). In lead polynuropathy, calcium disodium edetate (Versenate®) may be beneficial. In arsenical polynuropathy, give dimercaprol (BAL).

**Attempt to obtain optimal metabolism of nerve tissue by giving a high caloric diet and liberal use of vitamins, especially B complex.** The entire B complex can be administered with thiamine hydrochloride, 15 mg (1/4 gr) 3-4 times daily orally or parenterally, and dried yeast (brewer's yeast), 10-30 Gm (1/3-1 oz) daily.

**B. General Measures.** Place the patient at bed rest and forbid use of the affected limb. If a lower extremity is affected, keep a cradle over the foot of the bed to prevent pressure of bed covers. Give analgesics as necessary to control pain. After pain has subsided, massage and passive motion may be of value. Encourage active motion at the same time. Prevent contractures by means of splints and passive stretching.

#### Prognosis

In most forms of polynuropathy, recovery may occur once the cause has been corrected. In some cases the disorder progresses for weeks, remains stationary for a time, and goes on to slow recovery in 6-12 months. Objective sensory changes usually disappear first, and paralysis later, dysesthesias may persist during recovery.

Low, N. L., & others. Polynuropathy in children. *Pediatrics* 22:972-90, 1956.

Osler, L. D., & A. D. Sidell. The Guillain-Barré syndrome: the need for exact diagnostic criteria. *New England J. Med.* 26:964-9, 1960.

Sullivan, J. F. The neuropathies of diabetes. *Neurology* 8:243-9, 1958.

#### PERIPHERAL NERVE INJURIES

**Peripheral nerve injuries, ranging from simple contusions causing temporary dysfunction to complete anatomic section causing total cessation of function, may occur with lacerations, bone fractures, crushing injuries, or penetrating wounds. In the acute early phase, associated tissue damage, pain, and other circumstances may interfere with tests of motor or sensory function. Tinel's sign (a tingling sensation in the distribution of an**

affected nerve) may be elicited after the acute phase by percussion of the nerve or adjacent areas. In some old nerve injuries, trophic changes affecting the nails and skin, as well as painless skin ulcers, may be noted. Electrodiagnostic tests may be helpful in assessing the degree and nature of the neural deficit.

Treatment depends upon many factors, including the time and type of nerve injury, associated defects, and the general condition of the patient. When possible, end-to-end anastomosis of acutely severed nerves should be attempted. In old nerve injuries, good results are possible as long as 1-2 years after injury, when lytic of a scar, resection of a neuroma nerve transplants, and other surgical procedures may be attempted.

La Flia D J S Weir Mitchell on gunshot wounds and other injuries of nerves  
Neurology 5 468-71, 1955

## NEUROMUSCULAR DISORDERS

The neuromuscular disorders include a number of chronic diseases which are characterized by a progressive weakness and atrophy of certain groups of muscles. It is important to differentiate atrophies from dystrophies. Muscular atrophies result from a neural lesion involving either the cell body or axon of the lower motor neuron. Muscular dystrophies result from primary disease of the muscle itself.

Differential Diagnosis  
of Atrophies & Dystrophies

Atrophies	Dystrophies
Generally occur late in life	Occur in childhood
Affect distal muscle groups e.g. the small muscles of the hand	Affect the proximal muscle groups e.g. the hip and shoulder girdle
Show fasciculations	No fasciculations
May show spastic phenomena	No spastic phenomena
No familial incidence	Generally familial

## PROGRESSIVE MUSCULAR ATROPHIES

The progressive muscular atrophies are due to nuclear involvement of the lower motor neuron by progressive lesions. Since the causative agent is usually not known, the classification has been based upon the level of involvement rather than upon etiology. There is no treatment.

### Spinal Types

A Aran-Duchenne atrophy (myelopathic muscular atrophy) is the adult form of progressive spinal muscular atrophy. It is a rare disorder of middle age, starting in the small hand muscles with atrophy and fibrillations and slowly extending to involve the arm, shoulder and trunk muscles. A degenerative lesion is found in the cervical gray matter of the cord. It may occur as the first stage of an amyotrophic lateral sclerosis (see below).

B Werdnig-Hoffmann paralysis is a hereditary form of progressive spinal muscular atrophy occurring in children, starting in the pelvic girdle and thighs and spreading to the extremities. Associated adiposity may produce a pseudohypertrophy.

C Oppenheim's disease (amyotonia congenita) is considered by some to be a fetal form of spinal muscular atrophy due to growth abnormalities.

### Bulbar Types

A True bulbar palsy is caused by a nuclear involvement of the last 4 or 5 cranial nerves and characterized by twitchings and atrophy of the tongue, palate and larynx, drooling, dysarthria, dysphagia, and finally respiratory paralysis. True bulbar palsy is usually a manifestation of amyotrophic lateral sclerosis.

B Fazio-Londe atrophy is a bulbofacial type of progressive muscular atrophy occurring in childhood.

### Pontile Type

Pontile atrophies produce a chronic progressive ophthalmoplegia (Von Graefe's disease) due to involvement of the nuclei of the eye muscles.

### Spastic Type Amyotrophic Lateral Sclerosis

This is a combined upper and lower motor neuron lesion which may involve either the spinal or bulbar level, or both. It is a chronic progressive disease of unknown etiology associ-



ated with fibrillation and atrophy of the somatic musculature. It is predominantly a disease of middle life, with onset usually between the ages of 40 and 60 years. Degeneration of the motor cells of the spinal cord and brain stem and, to a lesser extent, of the motor cortex may occur, with secondary degeneration of the lateral and ventral portions of the spinal cord. There may be spastic weakness of the trunk and extremities, with associated hyperactive deep reflexes and extensor plantar responses. If the fibers of the bulbar nuclei become involved, pseudobulbar or bulbar paralysis may appear. The initial symptom is often weakness and wasting of the extremities (usually the upper extremities). The course is progressively downhill without remission. The average duration of life from the appearance of the first symptoms is about 3 years.

#### Neural Form of Peroneal Muscular Atrophy: Charcot-Marie-Tooth Disease.

This relatively rare disease is characterized by clubbing of the feet and muscular wasting which begins in the legs and later involves the muscles of the distal portions of the thighs and upper extremities. Atrophy of the leg muscles gives a characteristic "stork-leg" appearance, atrophy usually starts in the intrinsic muscles of the feet and in the peroneal muscles. The onset of symptoms is usually before 20 years of age, but is sometimes delayed until 40 or 50 years. Objective loss of sensation occasionally occurs.

Eaton, L. M., & others: Symposium: Amyotrophic lateral sclerosis. Proc. Staff Meet. Mayo Clin. 32:425-62, 1957.

Lawyer, T., & M. G. Netsky: Amyotrophic lateral sclerosis: a clinicoanatomic study of fifty-three cases. Arch Neurol 69:171-92, 1953.

### PROGRESSIVE MUSCULAR DYSTROPHY

#### Essentials of Diagnosis.

- Onset in childhood or at puberty of weakness of the proximal musculature of the extremities
- Waddling gait and "climbing up" on body to attain upright position.
- Contractures, scoliosis, lordosis, diminished deep tendon reflexes.
- Involved muscle hypertrophic or atrophic.
- Heredofamilial trend.

Differentiate from the muscular atrophies, which begin distally and may be associated with sensory loss and fibrillation. In muscular dystrophies the affected muscles waste longitudinally, in atrophies the wasting is often in stocking or glove distribution.

#### General Considerations.

The most common of the muscular diseases is progressive muscular dystrophy. Two principal types are recognized, depending upon the site of initial muscular involvement and the distribution of apparent hypertrophy and atrophy. In the pseudohypertrophic type (Duchenne) there is enlargement of the calves and sometimes the thighs. In the facioscapular type (Landouzy-Dejerine) the face and shoulder girdle are involved early.

The etiology is not known. A heredo-familial trend is usually noted. Various types of inheritance may occur: simple dominant, simple recessive, or sex-linked recessive.

The essential pathologic change is in striated muscle. In advanced cases, the affected muscles appear gray, white, and fatty.

#### Clinical Findings.

A. Symptoms and Signs. The onset usually occurs in childhood or at puberty. The child may waddle instead of walk, has difficulty climbing stairs, and may have difficulty in rising from the supine position on the floor. The child "climbs" up on his body with his hands or uses a support to pull himself upright.

Weakness of the proximal muscles of the extremities is characteristic. Weak muscles may appear to be hypertrophied or atrophied, and are apt to feel firm and dough-like upon palpation. Deep reflexes are usually diminished. Contractures frequently result as a consequence of unopposed muscle action. Scoliosis and lordosis, most pronounced on standing, are apt to occur.

B. Laboratory Findings. Biopsy of muscle may show fatty degenerative changes. The muscle fibers are swollen and large, and homogeneous in appearance with broken striations.

#### Differential Diagnosis

Progressive muscular atrophy develops later in life, beginning distally in the small muscles of the hand. Muscular fibrillation is present.

Dystrophic myotonia involves the sternomastoids, which are rarely affected in other dystrophies, and there is associated myotonia.

In peroneal muscular atrophy sensory changes are present, and involvement is first peripheral and gradually ascends

Progressive hypertrophic polyneuritis is characterized by distal involvement, sensory changes, and a thickened nerve

#### Complications & Sequelae.

Contractures commonly occur in the advanced stages. Pes equinus is due to calf muscle contracture

Respiratory complications, such as pneumonia, are apt to occur. There may be clinical or laboratory evidence of cardiac disease, probably due to intrinsic dystrophy of the myocardium

#### Treatment.

Supportive measures: physical therapy, and orthopedic devices may give some help and comfort

#### Prognosis.

The disease is usually progressive and greatly resistant to medical therapy. Patients may continue to show progression for 20-30 years. Patients become progressively weaker, ultimately being confined to chairs or beds

Dowben, R.M. • Diagnosis and treatment of disease of muscles. Arch Int Med 107 430-6, 1961

Fetterman, G.H., & others: Muscular dystrophy. J. Dis. Child, 91 326-44, 1956

Walton, J.N., & F.J. Natrass: On the classification, natural history and treatment of the myopathies. Brain 77 169-231, 1954

## MYASTHENIA GRAVIS

#### Essentials of Diagnosis

- Weakness of the bulbar-innervated musculature progressing as muscles are used (fatigue)
- Ptosis of lids, diplopia, facial weakness, weakness in chewing, swallowing, and speaking
- Positive neostigmine (Prostigmin®) and edrophonium chloride (Tensilon®) tests

Differentiate the weakness of the bulbar musculature from weakness associated with bulbar palsy (with its associated atrophies and CNS involvement), aneurysms of the circle of Willis (with its unilateral eye involvement), and functional disorders.

#### General Considerations.

Myasthenia gravis is characterized by marked weakness and fatigability of muscles, particularly those innervated by bulbar nuclei (face, lips, tongue, eyes, throat, and neck). It may affect practically any muscle in the body. The essential abnormality is considered to be impaired conduction of the motor nerve impulse at the neuromuscular junction associated with altered or excessive action of cholinesterase upon the acetylcholine liberated there. Although altered function of endocrine glands such as the thymus has been suspected of playing a causative role, the etiology remains unknown.

Myasthenia gravis is predominantly a disease of young people; it is more common in women between the ages of 20 and 40 years.

#### Clinical Findings

**A Symptoms and Signs.** The principal symptom is rapid development of fatigue and weakness of the affected muscles (especially those of bulbar innervation) with use. Diplopia is often present. Physical findings include the following: all of which are accentuated following use of the involved muscles: ptosis of lids, oculomotor muscle paresis and strabismus, "myasthenic smile," a nasal snarling smile, facial musculature devoid of wrinkles, difficulty in use and moving of tongue, high-pitched nasal voice, and difficulty in swallowing, chewing, or speaking. For example, after the first few swallows, difficulty in swallowing and regurgitation through the nose may occur; the voice may become nasal upon continued speaking.

**B Laboratory Findings.** In adults with myasthenia gravis, neostigmine methylsulfate (Prostigmin®), 1.5 mg ( $\frac{1}{40}$  gr.), with atropine sulfate, 0.6 mg ( $\frac{1}{100}$  gr.) (to prevent side effects), I.V., will produce a definite increase of muscle strength, sometimes of surprising degree. Edrophonium (Tensilon®), 2-10 mg I.V., produces a similar improvement within 1 minute; the improvement lasts only a minute or so.

**C Special Studies.** Repeated electric current stimulation of a myasthenic muscle shows decreasing intensity of contracture (fatigue). Repeated supramaximal stimulation of the peripheral nerve to affected muscles may cause a decline in the amplitude of their potential as noted on electromyograms.

#### Treatment.

**A Emergency Treatment.** Sudden inability to swallow or respiratory crises may occur at

any time. The patient should always carry 2 ampules of 0.5 mg ( $\frac{1}{120}$  gr) of neostigmine methylsulfate (Prostigmin<sup>®</sup>), to be given immediately subcut or I.M. if severe symptoms develop. He should be placed under medical care at once, if additional neostigmine is needed, 1 mg ( $\frac{1}{60}$  gr) may be given parenterally 2-3 times in one hour until an adequate response is obtained.

**Progressive and potentially fatal weakness** of the muscles of respiration may occur in spite of the administration of increasingly large amounts of neostigmine. A tracheostomy set, oxygen equipment, suction apparatus, and respirator should be available. After tracheostomy is performed, place the patient in a respirator and give oxygen as needed. Withhold neostigmine. Maintain fluid and electrolyte balance during the period of artificial respiration. After a few days, it is usually possible to gradually decrease the time spent in the respirator. In patients who survive the crisis remissions may occur, in some instances lasting for several years.

**B General Measures** Acquaint the patient with his disease, using simple lay terms. Maintain good nutrition and health.

#### C Specific Measures

1 Neostigmine bromide 15 mg ( $\frac{1}{4}$  gr) orally 4 times a day and increase (up to 180 mg/day) as required to give relief.

2 Pyridostigmine bromide (Mestinon<sup>®</sup>) an analog of neostigmine, is at times more effective in treatment of bulbar muscle weakness. Give 0.6-1.5 Gm daily at intervals spaced to provide maximal relief. Long-acting tablets (Mestinon Timespan<sup>®</sup>) 180 mg each are especially useful at bedtime.

3 Ambenonium chloride (Mytelase<sup>®</sup>) may act twice as long as neostigmine and has fewer side effects. Start with 5 mg t.i.d. and increase as necessary to give relief. The average dose is 5-25 mg q.i.d.

4 Edrophonium chloride (Tensilon<sup>®</sup>) may relieve myasthenic weakness. Ten mg I.V. gives relief in 20-30 seconds, 25-50 mg I.M. gives improvement lasting for hours. Two to 3 mg I.V. may be used as a test dose for patients under treatment to distinguish between myasthenic crisis (improves) and overtreatment (no change).

5 Ephedrine sulfate, 12 mg ( $\frac{1}{5}$  gr) with each dose of neostigmine often enhances the action of neostigmine.

6 Side effects of treatment with anticholinesterase drugs (e.g. abdominal cramps, nausea and vomiting) may be ameliorated or prevented by adding atropine or atropine-like drugs to the therapeutic regimen as necessary.

**D Surgery** Thymectomy has been said to benefit some patients, particularly young adult women.

#### Management of Newborn Infants of Myasthenic Mothers

Immediately after delivery, children of patients with myasthenia gravis may have severe signs of the disease. Immediate treatment with neostigmine is necessary to preserve life. After a few days the symptoms may disappear and the child thereafter usually does not suffer from myasthenia.

#### Prognosis

Spontaneous remissions occur frequently, but relapse is the rule. Pregnancy usually produces amelioration, although exacerbations may also occur at this time.

Myasthenic crisis, with sudden death from apparent respiratory failure, may occur. Survival of crisis may be followed by a remission. Overtreatment with neostigmine may produce muscle weakness simulating myasthenic crisis.

According to some studies the most critical period is the 2 years following onset.

Eaton, L. M. The clinical concept of myasthenia gravis. Proc Staff Meet Mayo Clin 23 1 7, 1948.

Grob, D. Course and management of myasthenia gravis. J.A.M.A. 153 529-32, 1953.

#### MYOTONIA CONGENITA (Thomsen's Disease)

Myotonia congenita is a rare hereditary disorder characterized by localized or generalized myotonia. Hypertrophy and hypertonicity of the muscles may occur, rendering them rigid and unyielding. The disease has occurred in five successive generations in the family of Dr. Thomsen, who first described it. Although it usually is not serious, the increased muscle stiffness makes it difficult for its victims to enjoy physical activity. Some have periodic attacks of generalized muscular spasm. Quinine sulfate 0.3-0.6 Gm (5-10 gr) 2-4 times daily has been used successfully in relieving hypertonicity.

Myotonia acquisita is a form of Thomsen's disease which has its onset late in life.

See references under Myotonia Atrophica, p. 464.

## MYOTONIA ATROPHICA (Dystrophia Myotonica)

Myotonia atrophica is a rare hereditary degenerative disease of adult life which appears to be a mixture of Thomsen's disease and muscular dystrophy. There is hypertonicity of some muscles usually of the tongue and the fist-making muscles of the hand together with atrophy and weakness of the face jaw muscles peronei and others. In both myotonia congenita and myotonia atrophica the patient characteristically grasps an object and then is unable to release his grip immediately. Myotonia muscle atrophy (especially of face and neck) cataracts early baldness testicular atrophy and evidence of dysfunction of other endocrine glands usually occur.

Maas O & A S Paterson The identity of myotonia congenita dystrophia myotonica and paramyotonia Brain 73 318 36 1950  
Pachomov N & J E Caughey Dystrophia myotonica Neurology 10 28 42 1960

## FAMILIAL PERIODIC PARALYSIS

Familial periodic paralysis is characterized by recurrent attacks of flaccid paralysis

of the muscles of the trunk and extremities and by a lowering of the serum potassium level during the attack. The cause is not known. Respiratory paralysis may occur and may be fatal if treatment is not prompt and adequate. Immediate relief of symptoms by administration of potassium chloride is usually diagnostic.

Treatment is with potassium chloride 5-10 Gm (75-150 gr) orally when diagnosis has been made and then 5 Gm (75 gr) 2-4 times daily during acute episodes as needed to prevent weakness or paralysis. In respiratory paralysis give a prepared solution containing 1 Gm (15 gr) potassium chloride in 50-60 distilled water very slowly I.V. Caution: This is a dangerous procedure.

Patients with this disease should avoid high carbohydrate foods. Routine administration of potassium chloride enteric coated tablets 8-12 Gm (120-180 gr) t.i.d. prevents attacks.

With adequate treatment the prognosis is excellent. Death may result from respiratory paralysis but this is rare.

Norris J H Some metabolic studies of sporadic and familial periodic paralysis Neurology 12 208 12 1962

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## Psychiatric Disorders

Harry K. Elkins

### GENERAL PRINCIPLES OF PSYCHIATRIC DIAGNOSIS & MANAGEMENT

For many emotional difficulties experienced by patients formal psychiatric diagnosis is not possible and specialized psychiatric treatment is not necessary. The physician who concerns himself with the emotional problems of his patients is practicing the art of medicine, which is as inseparable from the science of medicine as psyche is from soma. This means that the emotional component present in any physical illness must be handled with due care and consideration. The very presence of the physician offers reassurance, security, and hope, and what the physician does or says is often less important than how he does or says it. The "bedside manner" is not mere fiction, it cannot be affected or readily learned, but reflects the physician's own concern for his patient's total welfare. For example, the prescription of a placebo or "T L C" (tender loving care), the use of firm guidance or persuasion, admonition and direct advice, and sometimes "just listening" are all aspects of informal psychiatric treatment.

and emotional difficulties may themselves augment or precipitate physical dysfunction or pain. A vicious cycle or "closed circuit" may thus be set up so that the patient eventually loses the ability to function both physically and emotionally.

Anxiety and depression commonly accompany any physical illness. Both are discussed in greater detail below, but since the alleviation of anxiety and depression is often important in the treatment of physical illness it is well to keep the following in mind: (1) Physical illness often evokes feelings in the patient of helplessness and dependency. (2) A physical incapacity may be used unconsciously as an opportunity for secondary gain in the form of attention, love, special consideration, or pity. (3) A physical illness may be regarded by the patient (sometimes unconsciously) as deserved punishment for thoughts and feelings about which he feels guilty.

Feigning or exaggeration of physical illness may also be used, as in malingering, for the purpose of avoiding responsibility or for financial gain. In such cases anxiety and depression are not prominent features, and the tension present is more apt to be due to the malingerer's fears that his dishonesty will be exposed. He usually responds with anger when confronted with his failure to get well.

### ANXIETY

Anxiety, as the term is used in psychiatry, is fear in the absence of an external threat. It is sensed as an inner uneasiness, and may be brief and self-limited, sometimes felt as intense dread and alarm, or may assume panic proportions. Anxiety may be related to specific circumstances or objects (as a phobia), a specific body part or organ system (as in some forms of conversion hysteria or psychophysiological disorders), may be so vaguely fixed that the patient can only say, "I don't know why I feel so upset" (as in anxiety neurosis), may be the most outstanding early symptom of a psychotic break with reality (as in schizophrenic disorders); and may be accom-

- Castelnucovo-Tedesco, P : The 20 minute "hour." An experiment in medical education. *New England J. Med.* 266 283-8, 1962.  
Davis, H.K. : How to manage emotional problems in general practice. *GP* 26:106-10, 1962.  
Scott, W C M , & others : Panel on brief psychotherapy. *Canad Psychiat Assn J* 5 161-84, 1960.  
Terhune, W B : The management of the psychiatric patient in general office practice. *M.Clin.North America* 45:1589-94, 1961.

### EMOTIONAL FACTORS IN PHYSICAL ILLNESS

In many instances physical illness may increase or help precipitate emotional difficulties,

panied by asocial or hostile behavior (as in the sociopathic and character disorders). The patient may attempt to narcotize his anxiety with alcohol or other addicting substances, or may seek a more socially acceptable form of relief from anxiety through work, friends, and activities. Anxiety in any form must be dealt with promptly, since it is a common manifestation of many psychiatric illnesses.

Somatic complaints commonly associated with anxiety include palpitations, tachycardia, gastrointestinal spasms, diarrhea, constipation, muscle spasms, tremors, sweats, constrictions in the throat or other parts of the body, insomnia, and headache.

Restlessness, emotional discomfort even when alone, irritability, and difficulty in relationships with others are usually present.

Hordern, A : Psychiatry and the tranquilizers  
New England J Med 265:584-8 and 634-8, 1961.

Hope, J, M The anxiety state GP 24:134 42, 1961.

circumstances of the patient's life as well as current factors. In evaluating a patient's emotional responses to an illness the physician should consider how that patient has reacted in the past under similar circumstances and must consider the patient's total life situation (including family, financial, and other personal factors).

Depression and anxiety are frequently found together. Both must be treated since both are frequent features of more specific psychiatric illnesses.

Levy, S : Early diagnosis and treatment of depressive reactions Postgrad M J 31: 557-62, 1962

McGill University Conference on Depression and Allied States Canad Psychiat Assn J (Special Supplement) 4:S1-S197, 1959.

Stoeckle, J D , & G E Davidson. Bodily complaints and other symptoms of depressive reaction J A M A 180:134-9, 1962

## THE COMBINED MEDICAL & PSYCHIATRIC EXAMINATION

### DEPRESSION

Depression is a feeling of sadness, dejection, or despondency. Like anxiety, it may be present in many emotional disorders and may occur as a more or less normal reaction to life, e.g., whenever an important loss is sustained. Depression is normally encountered following the death of a loved one, following romantic disappointments, during the climacteric if physical, business, or sexual activity is interfered with, at retirement for some individuals, and during illness and incapacitation. The loss may be of a material nature or may consist of a reduction in status, or enforced separation from another person with whose life the patient's own is closely identified (e.g., a son or daughter going away to college). A more complete discussion of depression as it occurs in specific psychiatric illnesses is found on pp 478-80.

The practitioner commonly must deal with depression as a secondary factor after surgery or childbirth, when prolonged bed rest or dietary restrictions are necessary, and in association with disability.

The symptoms of depression include mood changes varying from insomnia and mild apathy to loss of motivation and suicidal thoughts or frank attempts to commit suicide. The extent to which even a mild physical illness may evoke a sense of failure depends greatly on the early

Psychiatric diagnoses must be based upon positive psychiatric findings and not simply the exclusion of organic findings. For this reason, the combined medical and psychiatric examination is of great importance in the evaluation of a patient with a suspected psychiatric disorder. Furthermore, a thorough history and examination may have considerable therapeutic as well as diagnostic value.

The interview should be conducted in a comfortable, quiet room without noise or interruption. After inquiring about the presenting complaint, the physician should permit the patient to tell his own story in his own way. The most appropriate attitude is one of patience, good will, and interest, unnecessary direct questioning and interpretative comment should be avoided. In most cases it is wiser to avoid writing while the patient is giving his history, especially those portions of the history which he may consider to be personal or confidential. Attempt to develop a retentive memory and write down or dictate pertinent information as soon as possible, but preferably not in the patient's presence.

It is important to determine the patient's real reason for seeking medical assistance. The presenting complaint may not be the real reason, or the appointment may have been made at the insistence of the wife or husband. Allow the patient complete freedom in develop-

ing his history. If he should pause, encourage him to continue by an appropriate word, expression, or gesture.

A relaxed examination of this sort will frequently elicit pertinent information which would not have been drawn out by direct questioning. It also helps to establish a comfortable doctor-patient relationship which will be useful in further treatment. If the patient resists giving information on questioning in a certain area it is best to postpone further discussion of that topic until the relationship is more firmly established. Long, rambling discussions may be controlled by subtly interjecting questions about the patient's illness or his reaction to it. Less pertinent questions can be asked and bits of information pieced together at subsequent visits.

It is not necessary at this point that the physician "do" something in order to effect treatment, it is frequently sufficient that he listen attentively. The patient's use of particular words and expressions may help to identify the recurrent theme of his feelings. The patient will generally convey his unconscious feelings, often hidden behind strong defenses such as rationalization or projection. His feelings may be revealed not only with words but with many nonverbal clues as well: gestures, tones of voice, significant omissions, parrying of direct questions, and sudden shifts of subject matter as he breaks off a description of his headaches, for example, to mention an impending visit from his parents. Apparently inconsequential and irrelevant matter may be recognized by the physician as a deliberate or unconscious attempt to divert discussion from a painful area. In all this the physician's objective can be stated quite simply: It is to understand his patient's feelings so that he may help the patient understand and accept himself.

At times it may be convenient or necessary to postpone the conventional medical history (e.g., past medical history and system review) to a later visit. Unless the patient is severely ill, the physical examination and other diagnostic studies may also profitably be postponed until the patient is reasonably at ease. The medical examination must be performed in such a way as to assure the patient that he is being well taken care of and that the physician takes his complaints seriously. However, elaborate and expensive x-ray, laboratory, or other diagnostic studies for the purpose of mere reassurance of the patient are not warranted.

## THE PSYCHIATRIC INTERVIEW

If it appears that the patient's problems are largely psychogenic, it is desirable to expand the history and examination to elicit further information of psychiatric interest.

(1) Hereditary factors: Family history of psychiatric illness.

(2) Environmental factors during development: Early childhood training and experiences, family and social relationships, important friendships, scholastic record, desires and interests, sex experiences and attitudes, vocational training and experience, personal ambitions, religious attitudes.

Certain childhood traits, especially when several are present, are highly suggestive of deep-seated neuroses: strong fears (e.g., of animals, high places, closed places, dark), thumb-sucking, nailbiting, temper tantrums, bedwetting, sleepwalking, stammering, nightmares and night terrors, dizziness, fainting, convulsions, tics, and sulking. Also to be considered are difficulties in adjusting with peers, failure to accept authority, clinging over-dependency, and overtly aggressive behavior.

(3) Precipitating factors: Most important are romantic or sexual difficulties, domestic and occupational problems, financial reverses, anxiety over health, upheavals in way of living, deaths in the family, and overwork and fatigue.

(4) Mental status: Unusual somatic complaints are frequently encountered in both neuroses and psychoses. Observe general behavior (appearance, speech, actions and attitudes), mood (anxiety, agitation, elation or depression), thought content (illusions, delusions, or hallucinations), and sensorium (insight, intelligence, orientation, and memory).

### Special Diagnostic Aids.

In addition to the psychiatric evaluation approached by means of the interview, several additional diagnostic procedures may be useful. These should be performed and interpreted by specialists in their respective fields.

A. Electroencephalographic Studies (EEG). Useful in helping to differentiate organic from functional types of disorders, identifying convulsive seizure problems, etc.

B. Psychometric Testing. Useful in helping to differentiate organic from psychogenic disorders, measuring intelligence and special abilities, and in gaining information about the patient's personality, feelings, and psychic problems.



1. Objective tests - These provide a quantitative evaluation of personality traits or abilities as compared with established norms.

a. Intelligence tests (e.g., Wechsler-Bellevue, Stanford-Binet).

b. Minnesota Multiphasic Personality Inventory (describes 9 levels of personality categories: hypochondriasis, depression, hysteria, masculinity-femininity, schizophrenia, etc.).

c. Vocational aptitude and interest tests.

2. Projective tests - These attempt to evaluate the patient's feelings through his responses to stimuli which may be variously interpreted. Many such tests have been devised. Two of the more commonly used tests are the Rorschach test (inkblots used as stimuli) and the Thematic Apperception Test (TAT; unstructured or ambiguous pictures used as stimuli).

Psychologic testing is indicated in the following circumstances:

(1) For children:

(a) Wherever a question of mental retardation is present.

(b) To determine IQ, scholastic deficiencies, and "grade age."

(c) For adoption purposes or when commitment or sterilization is contemplated.

(d) As an adjunct (along with EEG studies) to the physical examination and history to help identify or rule out a possible organic cause of certain behavior problems (Psychologic tests are not very useful for this purpose in children under 9 years of age.)

(2) For adults:

(a) As an adjunct to psychiatric diagnosis. They may be especially useful in helping to differentiate organic from nonorganic problems, and are also helpful in ascertaining the presence and degree of schizophrenic thinking.

(b) To help determine psychodynamics, the depth of psychiatric treatment indicated, and the suitability of psychoanalysis.

(c) To estimate the validity of unusual mental phenomena (e.g., some apparently delusional or paranoid material may be real).

(d) For vocational guidance, identification of aptitudes, skills, and interests.

## PSYCHOGENIC vs. ORGANIC ETIOLOGY

Since psychiatric disorders may have somatic manifestations and since organic disease may have psychic manifestations, the differentiation of psychogenic ("functional") from organic disorders may be difficult. The

difficulty stems in part from the patient's reluctance to admit that his illness, which may indeed be disabling, is "imaginary" or of an emotional nature, and the clinician's natural reluctance to ascribe an illness to psychogenic factors solely on the basis of absence of organic findings even when psychic features are evident. The problem is further complicated by the fact that the initial phase of certain serious organic disorders may be insidious and occult, and objective medical findings may be equivocal or absent.

The following may be helpful in differentiating psychogenic illnesses from those of organic origin: (See also the table on p. 489.)

(1) A history of anxiety or unusual behavior since childhood.

(2) Multiplicity of symptoms involving many organ systems

(3) Preoccupation with bodily functions and morbid fear of disease.

(4) Bizarre symptoms (unusual location, character, and severity) and atypical response to treatment

(5) History of "physician-shopping" and failure to follow through any recommended treatment.

(6) Absence of objective medical findings, or symptoms out of proportion to medical findings.

(7) Absence of concern or anxiety in the face of apparent disability (e.g., "paralysis").

(8) Onset or aggravation of symptoms coincident with anxiety or stress situations.

(9) Secondary gain considerations (e.g., attempts to utilize "illness" unconsciously or consciously to attract attention, obtain sympathy, evade responsibility, or collect insurance).

(10) Dependence upon a variety of medications, including alcohol, to relieve distress.

## PSYCHIATRIC CLASSIFICATION

In the actual practice of psychotherapy diagnostic labels are often set aside completely in favor of understanding the patient in common sense terms. As long as the physician maintains a neutral attitude and helps the patient deal with problems in his current life with sympathetic understanding, a great deal of benefit can be obtained, for example, from simple ventilating sessions.

However, for the purposes of formal professional communication specific diagnoses are often desirable and necessary, and numerous attempts have been made to organize the

# Standard Classification of the American Psychiatric Association (Abridged)

## A. Disorders of organic or toxic origin

### 1 Brain disorders (acute and chronic)

### 2. Mental deficiency

## B Disorders without clearly defined physical causes, i.e., those of psychogenic origin

### 1 Psychoneurotic disorders (the neuroses)

- a. Anxiety reaction (anxiety is diffuse or "free-floating")
- b. Dissociative reaction (fugue, amnesia, dream state episodes)
- c. Conversion reaction (anxiety is displaced to an organ or part of the body)
- d. Phobic reaction (anxiety is fixed upon a specific idea, object, or situation)
- e. Obsessive-compulsive reactions (anxiety results in repetitive thoughts and acts)
- f. Depressive reaction (unconscious anger and the associated anxiety are partially relieved through self-deprecation)

### 2 Personality and personality trait disorders (character disorders)

- a. Inadequate personality (inadaptability, poor judgment, social incompatibility)
- b. Schizoid personality (aloof, emotionally detached, autistic)
- c. Cyclothymic personality (alternating moods of elation and sadness)
- d. Paranoid personality (suspicious, envious, jealous, stubborn)
- e. Emotionally unstable personality (reacts to life with excitability and ineffectiveness)
- f. Passive-aggressive personality (basic reaction to life is with dependency or aggression)
  - (1) Passive-dependent type
  - (2) Aggressive type
  - (3) Passive-aggressive type

### 3 Sociopathic personality disturbances (gross social maladjustments)

- a. Antisocial personality and dyssocial personality (formerly known as psychopathic personalities)
- b. Sexual deviate (homosexuals, transvestists, sexual sadists, etc.)
- c. Alcohol addiction
- d. Drug addiction

### 4. Psychophysiologic autonomic and visceral disorders (psychosomatic disorders): Organic and physiologic changes occur in the musculoskeletal, respiratory, cardiovascular, gastrointestinal, genitourinary system, etc., due to psychogenic factors

### 5. Psychotic disorders (the psychoses)

- a. Involutional psychotic reaction (involutional melancholia)
- b. Manic-depressive reaction (manic type or depressed type)
- c. Psychotic depressive reaction
- d. Schizophrenic reaction (simple, hebephrenic, catatonic, paranoid, mixed)

### 6 Transient situational personality disorders (reserved for those cases which seem to be an acute response to external precipitating stress and in which no underlying previous personality disturbance appears to be present)

psychiatric disorders into a single classification system which would include both etiologic and descriptive information as well as give some indication of psychodynamics, i.e., what is "going on" in the patient's emotional life or what his "essential feeling theme" is likely to be. Other important considerations in any system of classification involve the question of the principal mechanisms of defense which the patient uses (e.g., denial, repression, projection) as well as the stage of personality development to which his character has apparently regressed. So much overlapping of symptoms, dynamics, and etiology occurs that it is impossible at present to evolve an ideal system of classification. Most psychiatrists in the United States, however, for administrative and legal purposes, report their observations in terms of the *Standard Classification of the American Psychiatric Association*.

The current tendency is to designate the psychogenic disorders either as types of reaction, e.g., depressive, obsessive-compulsive, schizophrenic, or as personality types, e.g., passive-dependent, compulsive. The use of the terms "reaction" and "personality" more correctly indicates that the patient's illness is his own unique response to anxiety or manner of adjustment, and avoids the unwarranted implication that the patient suffers from a concrete entity which is at least suggested in such statements as, "The patient has schizophrenia."

Beck, A. T., & others: Reliability of psychiatric diagnosis. *Am J Psychiat* 119:351-7, 1962

Diagnostic and Statistical Manual for Mental Disorders. American Psychiatric Association, Mental Hospital Services, 1952

## GENERAL COUNSELING

The physician is frequently called upon to provide emotional support and give advice about such matters as childbirth and child-rearing, adolescent adjustment, sexual and marital problems, and even personal and business frustrations and the difficulties of adjusting one's inner desires to the real world. A healthy personal philosophy, a thorough knowledge of the patient as a person and of his family and background, and plain common sense will enable the physician to assist most patients to work out their own solutions to these problems. Along with the clergyman, the physician can be of great help to his patients during times of stress, and can thus help to prevent many se-

vere psychiatric disorders. In each case consideration of the patient's total life situation, his past psychic experiences, and his mode of relating to others are important.

The physician must also bear in mind that a disturbed patient's feelings and behavior, although they may be troublesome to the patient and to others, are due to causes, often obscure, which are beyond the patient's control. Exhortations to exert "will power" or to "snap out of it" are generally futile and may be harmful.

Many of the emotional reactions in the adult which the physician must understand and treat represent regressions to childish or infantile patterns of thought and behavior which often seem inappropriate or bizarre. Unfortunately, the intellectual acceptance of this explanation by the patient does not necessarily help him.

## Counseling of Families.

In many child-parent and husband-wife problems the difficulties lie in the failure of one or both parties to fulfill the other's emotional expectations. Dependent or hostile feelings may be acted out by one party upon the other. In some cases each party becomes sensitized and reacts to the emotions of the other in such a way that mutually destructive behavior results. In these cases the physician faces the difficult task of dealing with 2 or more individuals and their feelings and responses to each other. It may be possible to educate the individuals so that each can recognize the "game" both are unconsciously playing and the harm that is being done.

The more skillful and intrepid practitioner may attempt to counsel both partners, separately and together, and some psychiatric specialists in this field will counsel the entire family as a group ("family therapy"). In some cases it might be better to recommend that another therapist treat one of the parties so that a "triangular" situation can be avoided. Whatever counsel is offered should be stated in positive terms which are ego-strengthening rather than in negative or critical phrases. Emphasis should be placed on the strengths which already exist rather than on personality weaknesses.

Ackerman, N. W.: *The Psychodynamics of Family Life*. Basic Books, 1960

## Countertransference.

In most professional situations involving the emotional management of his patients the physician may expect to move with ease and effectiveness depending upon his interest in

and knowledge of the field his personal ability and desire to be of service and the time available. However the physician must remember that it is his interest and knowledge but not his personal involvement that are the basis of sound medical treatment. The physician may unconsciously assume certain attitudes toward the patient (e.g. attempting to correct, teach, punish, rescue, or feel close to him) which serve his own emotional needs (countertransference). These feelings may seriously interfere with treatment. Unless the physician can extricate himself from emotional involvement with his patient by adopting a more objective attitude he would do well to refer the patient to someone else for help. Referral should not be postponed for fear of offending the patient or his family because of a misconception of the cost and nature of psychiatric help or because of the physician's unwillingness to admit failure.

### MANAGEMENT OF SITUATIONAL DISORDERS

In addition to permitting the patient to tell his troubles (mental catharsis) the practicing physician can deal with many emotional problems due to environmental maladjustments in the following ways:

- (1) Determine the patient's reasons for reacting to his situation in emotionally disturbed ways. If the patient is assisted in facing his problems objectively, an altered philosophy or change in attitude may make his situation more tolerable.
- (2) Help the patient to correct or alleviate situational factors. Utilize religious, legal, social service, or welfare agencies as indicated. The patient's family or associates can be approached (with the patient's consent) to obtain additional information and can often be persuaded to make favorable changes in the patient's environment. Assistance may sometimes include recommendations for changes in environment, marital status, or occupational status, but drastic changes of this sort are often impossible and may complicate rather than simplify the patient's problems. Help the patient to find his own solution but do not attempt to make decisions for him.
- (3) Utilize sublimating (diverting) techniques. Encourage the patient to develop other interests and skills (e.g. sports, hobbies) particularly when he has excessive time for self-preoccupation. At times it is helpful for the patient to offer services to others. This is

both an opportunity for unselfish expression and a means of obtaining approbation.

(4) Adopt a kindly attitude. Reassurance, suggestion, persuasion, and even admonition may be useful as the case demands. Avoid reproaching or arguing with the patient.

### MANAGEMENT OF DEEP SEATED NEUROSES

(Chronic Emotional Disorders Due Mainly to Internal Conflicts)

Re-education or reorientation techniques are best left to the psychiatrist. If psychiatric help is not available, symptomatic and supportive medical measures deserve the greatest consideration.

#### Precautions

- (1) Avoid brutally confronting the patient with possible causal factors of neurotic symptoms.
- (2) Avoid premature interpretation of psychiatric data.
- (3) Avoid anger toward the patient because of failure of improvement.
- (4) Avoid aggressive psychotherapy during the acute or symptomatic phase of the patient's disease.

### PSYCHIATRIC REFERRAL

#### Evaluation of Patients to be Referred

Most neurotic patients and some psychotic patients may be helped considerably by the physician who is interested in his patient's emotional problems and is willing to devote the time and has the necessary training and ability. As a matter of fact, such patients constitute a significant portion of the practice of most physicians. However, when the cause of the patient's symptoms remains obscure or when symptoms are disabling or persistent in spite of the common sense insights, counseling, and medical treatment which the physician can provide, some type of psychiatric intervention should be sought.

Psychiatric referral should be considered in the following circumstances:

- (1) Whenever it is feared that the patient may harm himself or others.
- (2) When anxiety and depression do not readily respond to informal psychotherapy and medical treatment.

(3) When disturbances in mood, thinking, or behavior are prolonged, out of proportion to apparent cause, or so acutely bizarre as to suggest significant psychiatric disturbance.

(4) When paranoid thinking or behavior is present.

(5) When physical dysfunction or pain is present for which no organic basis can be discovered.

(6) When specific phobias (irrational fears) or compulsions tend to cripple the patient or limit his effectiveness in any area of adjustment.

(7) When sexual aberrations (including impotence and frigidity) are present.

(8) When drug or, in many cases, alcohol addiction is present

#### Preparing the Patient for Referral.

When the clinician feels that psychiatric referral is necessary, he should explain the need carefully and tactfully, in a matter of fact manner, without apology and without misrepresentation. If the patient has psychosomatic complaints the physician must explain their possible emotional origin as well as he can, showing at the same time that he understands that the pain or disability is just as severe and just as "real" as if it were due to organic disease.

It may be necessary to enlist the support of the patient's relatives or friends, particularly if the patient lacks insight or if he shows considerable resistance to psychiatric referral.

After referral, the physician's continued interest in and contact with his patient - at least until rapport with the psychiatrist has been established - may contribute greatly to the success of psychotherapy. In most instances the referring physician makes the initial contact for the patient. At times the patient may select from 2 or more psychiatrists suggested by the physician. In either case some degree of verbal or written communication between the referring physician and the psychiatrist may be expected.

Lemere, F., & A.B. Kraebel: The general practitioner and the psychiatrist. *Am. J. Psychiat.* 116:516-21, 1959.

Reckless, J.B.: The physician's reaction to the patient with functional illness. *Rocky Mountain M.J.* 59:34-7, 1962.

Taylor, J.B.: The psychiatrist and the general practitioner. *Arch. Gen. Psychiat.* 5:1-6, 1961.

#### SPECIAL PSYCHIATRIC TREATMENT

The variety of schools of psychiatric theory which exist, along with a common notion that all psychiatric treatment is necessarily expensive, has led to some erroneous ideas regarding the usual methods of psychiatric practice. Many psychiatric problems require only short-term intervention and the cost is not prohibitive. No particular psychiatric school of thought has been shown on statistical or clinical grounds to give superior results, and most psychiatrists will use a number of techniques, procedures and medications along with the special kind of verbal relationship known as psychotherapy.

In many cases the patient's attitude toward the "stigma" often felt to be associated with psychiatric illness must be adroitly manipulated by the physician before referral can be accomplished. Unfortunately, many physicians have themselves not yet come to terms with the concept of the psychiatrist's role in the total health care of persons who are not strikingly "deranged." It is the duty and responsibility of psychiatrists and sympathetic physicians in their local communities to combat these unconstructive attitudes so that the undoubted benefits of psychiatric services can be made available to a wider segment of the patient population as a preventive mental health measure.

The use of appropriate medication or physical procedures is not necessarily contrary to psychiatric principles. Any approach which helps the patient become more amenable to psychotherapy, modifies symptoms, increases comfort, allays nontherapeutic anxiety, and prevents destructive behavior may be used. However, whatever procedures or medications are used are only adjunctive to the vital psychotherapeutic patient-doctor-relationship.

#### Common Adjunctive Psychiatric Techniques.

In addition to the verbal psychotherapeutic relationship, the most commonly used techniques of the psychiatrist include the following:

##### A. Somatic Procedures:

1. Electroconvulsive (ECT) and insulin therapy

2. Narcoanalysis and narco-synthesis (amobarbital (Amytal®) and thiopental (Pentothal®) interview).

3. CO<sub>2</sub> and sleep therapy (neither of these have gained wide acceptance in the U.S.A.).

4. Psychosurgery (lobotomy, prefrontal lobotomy, thalamectomy). These are rarely indicated.

5 Physical therapies (hydrotherapy cold pack continuous tub special exercises muscle relaxation heat massage)

B Hypnotherapy In the hands of (or under the supervision of) a qualified psychiatrist has special value in selected cases

C Medications Almost any type of medication may be used for psychotherapeutic purposes Not only the medication itself but the route selected oral or intramuscular may be selected for psychotherapeutic reasons

1 Sedatives hypnotics tranquilizing drugs

2 Antidepressants and stimulants

3 The value of lysergic acid diethylamide and other psychotomimetic drugs has not yet been adequately demonstrated

D A variety of activities may be used including daily mental hygiene techniques work therapy and educational vocational and recreational guidance Special advice may be given regarding dietary habits rest sleep and sexual activities

Kaufman M R Hypnosis in psychotherapy today Arch Gen Psychiat 4 30 9 1961

Kubie L S Hypnotism Arch Gen Psychiat 4 40 54 1961

### Psychotherapy

The psychotherapeutic relationship is developed differently with each therapist and for each patient The general purpose no matter what steps are taken first is to provide a feeling of well being encourage insight re direct harmful attitudes and foster emotional growth The psychiatrist does these things in various ways

A His sincere interest in and intelligent understanding of the patient's problems is an immediate source of support The first general rule in treatment is that the patient should not feel alone with his problem

B Ventilation by the Patient For many patients the act of ventilating their problems in the presence of an understanding physician is sufficient treatment in itself The patient feels he has rid himself of a problem and that he still is accepted without censure

C Abreaction In many cases the patient's feelings are so strong that they also must be relieved by expression in the presence of an accepting person Great relief may be obtained if the patient can also express his pent

up feelings through an outburst of tears anger or a show of frustration or sorrow

D Shift of Emphasis Patients will often be unaware of the real source of their emotional difficulties and tend to place emphasis on the wrong persons or areas of their lives Thus a wife may show considerable feeling about the manner in which her husband treats her without being aware that the husband represents other persons who have frustrated her in the past e g parents or older siblings The psychiatrist when he has sufficient clues to these possibilities will help the patient shift emphasis onto those areas of his life and those relationships in which the patient's feelings originated

E Interpretation and Insight The correlation of feelings with pertinent life situations so that a coherent pattern of repetitive situations and responses becomes discernible to the patient

F Reassurance Support Direction and Persuasion These techniques may be used whenever necessary to protect the patient reduce unnecessary anxiety and guide the patient toward an acceptance of himself

G The Transference Mechanism The patient should ultimately recognize that he tends to react emotionally to his psychiatrist in much the same way he has reacted to other important persons in his past The ultimate working out or resolution of this transference of feelings is one of the important aspects of analytically oriented psychotherapy including psychoanalysis

### Psychoanalytic Treatment

Psychoanalysis is useful for many of the psychoneurotic disorders It is probably less effective for personality disorders and is of questionable value in sociopathic disturbances and the psychoses Not all patients however even in the psychoneurotic group are suitable candidates for psychoanalysis Psychoanalysis is a demanding therapeutic venture which places heavy burdens on the patient's time (and purse) and in a sense his talents and intellectual resources also Only a person who is capable of making creative leaps between obscure relationships will benefit from deep analysis This implies the necessity for critical introspection a willingness to read and learn and a strong motivation for improvement Psychoanalytic treatment usually requires frequent sessions over a period of more than 1 2 years

## THE PSYCHONEUROTIC DISORDERS

### ANXIETY REACTION (Anxiety Neurosis, Anxiety State)

#### Essentials of Diagnosis.

- Acute attacks of increased anxiety, tension, and feelings of impending doom, often associated with various somatic symptoms, e g , chest tightness, breathlessness, choking, sweating and palpitation
- Physical findings of widespread autonomic excitation
- Often no evident external cause for anxiety attack
- Between attacks fatigue, weakness, nervousness, headache, and irritability

Individual symptoms and signs of anxiety may suggest similar manifestations of other diseases such as angina pectoris (chest and arm pain), thyrotoxicosis (nervousness, sweating), pheochromocytoma (hypoglycemia), bronchial asthma or heart failure (shortness of breath), and the menopausal syndrome (sweating, flushing, palpitations)

#### General Considerations

The anxiety state is characterized by a subjective feeling of apprehension or tension usually unrelated to appropriate external stimuli, and by the objective psychic reaction (autonomic excitation) of fear. Acute anxiety attacks usually last from a few minutes to hours, but the chronic anxiety state may last for months to years interspersed with acute attacks

The anxiety state may occur as an isolated psychiatric illness or may be a prominent component of many other psychiatric illnesses such as depression, schizophrenia, and hysteria

The etiology is not known, but it is felt that anxiety represents a response to danger, usually internal and symbolic

#### Clinical Findings

The acute attack usually begins with a sudden onset of fear accompanied by restlessness, increased tension, tightness of the chest, breathlessness, palpitation, sweating, flushing, tightness in the throat, and trembling. Hyperventilation is usually marked, and the

Psychoanalytic treatment will vary to some degree depending upon the personalities of the analyst and the patient. The use of free association to uncover unconscious feelings, including those expressed in dreams, is one of the principal techniques used in psychoanalysis. The development of a "transference neurosis," in which the patient reacts as though the therapist were the significant person (or persons) in the patient's earlier life, and the ultimate resolution of this transference neurosis, is one of its special features

Much of the point of view and many of the techniques of psychoanalysis have been absorbed into the practice of general psychotherapy. Various schools of psychoanalytic theory which previously focused on the importance of biologic factors and instincts as opposed to interpersonal or cultural factors have given way to a recognition that in actual treatment all forces and aspects of the patient's life—instinctual, interpersonal, cultural, and social—must be considered

Glover, E. *The Technique of Psycho-analysis*  
International University Press, 1955

#### Group Psychotherapy

Within the past decade, especially in the U S A and Great Britain, there has been wide interest in and use of group psychotherapy. Various forms exist for patients with special problems in common (e g , marital partners), groups of one sex only, or of both sexes, or of mixed types of emotional problems, etc. Group sessions are held at regular intervals and conducted by a trained group therapist. Groups of more than 10-12 persons are generally found to be unwieldy. The reactions and interactions of the group members are freely discussed with the objective of developing insights and learning to help each other

Westman, J C : An overview of group psychotherapy. *Arch Gen Psychiat* 2:271-7, 1960

alkalosis which results from the blowing off of  $\text{CO}_2$  results in tingling of the fingers, toes, and perioral area which may progress to tetany. The patient has an impression of "impending doom." The attack lasts from a few minutes to hours and is usually followed by weakness and exhaustion lasting hours to days. Between attacks the patient's condition may vary from entirely well to nervous, tired, and concerned about the possibility of a new attack. Attacks may occur rarely or in rapid sequence up to several per day.

In chronic anxiety the complaints are usually those of nervousness, irritability, restlessness, headache, insomnia, and fatigue.

Physical examination may reveal excessive perspiration of the hands or axillae, mild tachycardia, signs of tetany and tremors. Routine laboratory analyses are normal. Functional hypoglycemia may be present.

### Treatment & Prognosis

A complete medical investigation will assist the physician in reassuring the patient that no organic disease is present. It may be necessary to see the patient on subsequent visits for further reassurance. Instruction regarding the voluntary control of hyperventilation (holding the breath or rebreathing in a paper bag) and the use of mild sedatives will usually be sufficient supportive care in the majority of cases.

For more resistant cases, treatment is aimed along 2 lines: those measures taken primarily to relieve anxiety symptomatically, and those taken to effect a basic character change.

Symptomatic measures for the relief of anxiety are the various drug therapies: physical therapy, hydrotherapy, occupational therapy, and attempts to channel anxiety into useful, creative, and productive areas such as work, volunteer services, and hobbies.

The use of tranquilizing medications, especially the phenothiazines and meprobamate, is in vogue at present, but the dangers of toxicity as well as a tendency toward habituation in some patients cannot be overlooked. Tranquilizing medications should be employed only in conjunction with efforts to relieve stress and provide support in the usual ways. Acute anxiety and panic states may require parental phenothiazines, e.g., promazine or chlorpromazine, or the barbiturates.

Basic character changes can be brought about only by means of long-term psychotherapy, including psychoanalysis.

## DISSOCIATIVE REACTIONS & CONVERSION REACTIONS (Conversion Hysteria)

### Essentials of Diagnosis

- Usually in patients with immature, unsophisticated personalities, often under great stress, e.g., frequently noted in wartime among military personnel facing hazardous assignments.
- Indifference of the patient to his behavior or to the loss of function of the affected part.
- In conversion hysteria there is no correlation between symptoms and anatomic nerve distribution.

### General Considerations

The dissociative reactions and the conversion reactions are disorders in which part of the patient's behavior or motor function is split off or isolated from the rest of his personality. The split, however, is partial rather than complete fragmentation, as in the case of the schizophrenic reaction, and in general the personality remains intact. The isolated bit of behavior or motor loss is often expressed in a fashion which is bizarre or dramatic.

In the dissociative reaction the isolated phenomenon occurs in the behavior of the patient, e.g., as in the fugue state or amnesia. Rarely, a complete depersonalization or dual personality may occur, as in the well-known story of Dr. Jekyll and Mr. Hyde. In the conversion reaction the isolated disturbance occurs in the motor function of the patient, e.g., hysterical paralysis of a limb, psychic blindness or mutism, and hysterical convulsive seizures.

In both reactions the isolated symptom is due to highly charged anxiety surrounding some incident or set of circumstances in the patient's past life which has been completely repressed. The symptom itself or the organ selected for dysfunction has symbolic meaning. The paralyzed part may prevent the patient from action which he unconsciously does not want to perform and also symbolizes sexual organs and acts or hostile objects which frighten him. For example, the paralyzed hand or leg or the blind eye represents a sexual idea which the patient has repressed (phallus, masturbation, watching coitus, etc.).

Differentiation of the dissociative and conversion reactions from organic disease and psychosomatic illness is shown in the table on p. 489. It may be quite difficult to differentiate hysteria from malingering. Continued observation will often reveal the lowering of the



defenses of the malingerer when he feels he is not being observed

### Clinical Findings

The hysterical patient is usually simple, impulsive, immature, egocentric, and highly suggestible. The specific infirmity reflects lay misconceptions of the apparent illness: the entire limb is paralyzed rather than a specific muscle group, anesthesia does not follow nerve pathways but occurs in stocking or glove distribution, and amnesia is usually restricted to a circumscribed series of events. Of greatest importance, however, is the patient's lack of concern about his infirmity ('la belle indifference').

When these patients have hysterical convulsive seizures they remain conscious, do not injure themselves, and are not incontinent of urine or feces. Hysterical motor tics involve coordinated groups of muscles and differ from organic tics. In the hysterically paralyzed limb vasomotor disturbances may occur, the limb may be blue and cold, and dermatographia may be present.

### Treatment & Prognosis

In some cases of conversion reaction or dissociative reaction removing the patient from a threatening situation will completely relieve symptoms.

Disappearance of symptoms such as hysterical paralysis, blindness, aphonia, and anesthesia may sometimes follow strong authoritative suggestion with or without hypnosis. Permanent cures are difficult to achieve in this way, however, for selected patients the dissociative and conversion reactions are often best treated with psychoanalysis.

Kiersch, T. A. Amnesia: a clinical study of 98 cases. *Am J Psychiat* 119:57-60, 1962.  
Ziegler, F. J., & others. Contemporary conversion reaction: a clinical study. *Am J Psychiat* 116:901-10, 1960.

### PHOBIC REACTIONS

A phobia is an intense dread, fear, or panic fixated upon a specific idea or thing. Many specific phobias have been described. Some of the more common ones are fear of high places (acrophobia), enclosed places (claustrophobia), open spaces (agoraphobia), cancer (carcinophobia), dirt, filth, or feces (coprophobia), cats (galeophobia, gatophobia),

death and dead bodies (necrophobia), and dark (nyctophobia). The particular thing, circumstance, or abstraction which provokes the reaction is a symbol of the fear of something else in the patient's unconscious life. For example, the patient who becomes anxious in enclosed places may in this way be expressing his aversion to being "trapped" in an unsatisfactory life situation (job, marriage, etc.) or his resentment of parental control in childhood. Fears of cancer, dirt, and death may represent unconscious hostile feelings toward specific persons or situations in his past or present life.

### Treatment

Persuasive techniques and building up the patient's self confidence so that he can gradually desensitize himself to his phobia are useful in a few cases, hypnosis has also been reported as "curative." Most cases, however, require total character reorganization through prolonged psychotherapy. When the patient is not motivated for insight psychotherapy, little more can be offered than persuasion, recondition, and gradual desensitization.

## OBSESSIVE-COMPULSIVE REACTIONS

### Essentials of Diagnosis

- Repetitive uncontrollable thoughts (obsessions) and acts (compulsions)
- The thoughts and acts are usually recognized as illogical and may be repulsive to the patient
- The patient is usually a meticulous, intelligent, insecure person

Compulsions and obsessions may also occur in paranoia, schizophrenia, and manic-depressive reactions, but in these conditions there is no recognition by the patient that his behavior or thoughts are absurd.

### General Considerations

The obsessive-compulsive reaction is a disorder in which constantly recurring thoughts or acts intrude upon otherwise normal thinking or behavior. The intrusive thought or action is alien to the situation and the patient feels a compelling need to think about the specific thought or perform a specific act in order to relieve his anxiety. It is believed that this type of reaction is the result of harsh discipline in childhood, beginning with early toilet

training and continuing with undue stress on neatness, cleanliness, punctuality, and memory (i.e., attempts to make the child conform to adult standards of behavior). In its mildest form this type of repetitive action or thought is universal, e.g., the persistent recurrence of a musical theme or a group of words, and is not considered pathologic. Only when these traits become exaggerated to the point of intruding upon the normal life of the individual and making him subservient to them are they considered abnormal.

Obsessive-compulsive reactions may occur in any age group.

#### Clinical Findings.

The obsessive-compulsive patient is usually highly intelligent, sociable, agreeable, pleasant, precise, oversensitive, shy, and self-conscious, and feels inadequate and insecure. His life is one of order and regularity. The obsessions and compulsions, however, are quite distressing. The patient realizes that they are illogical, but he feels anxious until he performs the compulsive act and performing it relieves his tension. His obsessions may interrupt his thought so frequently that he is incapable of productive thinking. The obsessions may be thoroughly distasteful to the patient, e.g., "indecent" thoughts, or thoughts about injuring another person. Repetitive handwashing, stepping on all the cracks in the sidewalk, and counting the windows of buildings are a few examples of compulsive behavior.

The obsessive-compulsive state is frequently accompanied by restlessness, irritability, tension, weakness, and fatigue as a result of the struggle to resist awareness of obsessive thoughts or the impulse to compulsive behavior.

#### Treatment & Prognosis.

Treatment is usually very difficult and must be undertaken by a psychiatrist. In adolescents and young adults some relief may be achieved by psychoanalysis. In children the prognosis is grave. Often the patient will obtain some relief by discussing his symptoms with the physician.

One of the most important things the physician can do is to point out that the symptoms are not due to supernatural forces but follow the laws of cause and effect. Only by understanding the relationship between events in his past life and his present feelings and the compulsive acts or obsessive thoughts can the patient free himself from them.

Even with treatment there is a tendency toward exacerbations and remissions, which in itself makes evaluation of therapy difficult.

## DEPRESSIVE REACTIONS (Psychoneurotic Types)

Depression is a mood of sadness, dejection, or despair. The intensity and duration of this mood varies considerably depending upon the personality background, the precipitating factors, and the current life situation of the patient.

Depression may occur at any time from childhood to old age, but is most common during adolescence, during pregnancy and immediately following childbirth, at the climacteric (in both men and women), and in old age. In many instances a feeling of "going it alone" is present.

Frequent findings are those of a general pessimistic attitude, feelings of hopelessness and failure, apathy, fatigue, loss of interest in the environment, sleep disturbances, loss of appetite and weight, diminution of sexual interest, and vague somatic complaints. Difficulties in concentration and reduced psychomotor activity are present, and the patient frequently "looks unhappy" although he may assume a feigned cheerfulness.

Constipation, dryness of the mouth, anorexia, amenorrhea, and impotence or frigidity are sometimes present.

#### Classification

##### A Primary Depression:

1. Grief reactions or acute situational reactions - These are often self-limiting, and occur in response to recent loss or frustration.

2. Reactive or neurotic depressions - These may be precipitated by circumstances in the immediate environment, but the depressive response is often out of proportion to its cause and is augmented by earlier loss or feelings of self-deprecation.

3. Manic-depressive reactions - Many of these do not reach psychotic proportions but are exaggerations of a basic cyclothymic personality with profound mood swings.

4. Involuntarily depressive states (Involuntary melancholia)

##### B Secondary Depressions:

1. Associated with various physical illnesses or incapacity.

2. Associated with toxic states (e.g., alcoholism).

3. Associated with organic brain disease.

4. Associated with schizophrenia - In some cases depression may be the outstanding symptom preceding an acute schizophrenic reaction.

### Diagnosis of Primary Depressions.

A. Grief Reactions (Acute Situational Reactions): Loss is usually experienced through the death of, separation from, or rejection by a person with whose life the patient's own has been closely identified. Career disappointments may also result in this type of depressive response. Denial of the loss through expressions of hostility and general irritability may be present. Sleep and appetite disturbances are common but generally mild, and suicide is not a prominent risk.

B. Reactive Depressions (Neurotic Depressive Reactions): Precipitating factors are not always readily discernible, or may seem to be too minor to account for the profound or prolonged reaction which results. There is usually a long history of neurotic symptoms in which anxiety has been the outstanding component. In many cases it appears that a disappointment or failure acts merely to open the door to existing unconscious feelings of rejection and failure. The symptoms and signs of acute situational depression are also present in the reactive depression. Sleep disturbances with troublesome dreams are common since these patients usually have had unconscious negative images of themselves for a long time. Awakening during the night (sometimes in the early morning hours), with anxiety to the point of agitation, occurs frequently, and the patient has difficulty getting up in the morning to face another day. Crying spells, especially in women, and a deep sense of guilt mark the course of many neurotic depressions.

Good contact with reality is maintained, and although work function is impaired these persons are generally able to continue their daily lives.

### Treatment.

The physician may empathize with but not sympathize with the patient. The difference lies in giving support and understanding without giving the patient further reason to feel sorry for himself. Psychotherapy is provided for the purpose of encouraging insight into early as well as present causes of the patient's negative self-image. Creative and productive pursuits should be recommended to assist the patient to adopt a more positive attitude toward his personal value. Specific advice should be given on how to make creative readjustments at work and at home.

Primary depressions are usually self-limiting. Antidepressant drugs and other medications as indicated should be given to ensure sufficient sleep and to reduce anxiety during the day.

Psychotherapeutic referral is indicated if suitable readjustment seems to be impossible for those patients whose anxiety becomes overwhelming.

Treatment of secondary types of depression consists of general psychotherapeutic support and antidepressant medications along with specific attention to the primary illness.

Patients with prolonged and disabling depressions who do not respond to the kinds of treatment described above may be suitable candidates for ECT (see p. 491).

The treatment of manic-depressive reactions and involuntarily depressive states is discussed on pp. 494 and 493.

Freyhan, F. A. · The modern treatment of depressive disorders. *Am J Psychiat* 116:1057-64, 1960.

Martin, H. B. · Specific diagnosis of psychoneuroses. GP 24:96-100, 1961.

Rogers, D. M. (editor). · Depression and antidepressant drugs. A conference at Metropolitan State Hospital, Massachusetts Department of Mental Health, 1960.

## POSTPARTUM DEPRESSION

The postpartum period is complicated for some women by feelings of depression and despair about the role of being a mother. Rumination and a feeling of being trapped, with resentment toward the baby and the husband, can make this a difficult time, especially for a woman with a passive-dependent personality structure or one who feels that marriage and motherhood have frustrated her desires for other types of fulfillment in life.

The course of the prenatal period is no direct indication of the degree of depression and anxiety which may occur after delivery since much depends on what "being a mother" may mean to some women. For example, it implies, "Now I am tied down, prevented from the satisfaction of other desires and the pursuit of other goals". If it evokes unpleasant memories of her own mother, or if the patient feels she should have presented her husband with a son instead of a daughter, she is apt to respond with a varied emotional picture in which depression is the outstanding feature.

Strangely enough, psychotic reactions are more common among multiparas. Because motherhood often represents the necessity for making decisions for another human being, the incidence of postpartum depression is greater among passive-dependent women, who feel un-

consciously inadequate about themselves and lack strong key persons to whom they can turn for emotional support

The treatment of postpartum depression may require considerable attention by the physician as well as his support as a substitute parental figure. Profound or prolonged postpartum depression is an urgent indication for psychiatric consultation, especially when anxiety is acute or psychotic elements are present. In occasional cases postpartum depression may assume the proportions of a full-blown manic-depressive or schizophrenic reaction, in which case ECT is generally effective.

Bushnell, L. F.: First trimester depression: a suggested treatment. *Obst & Gynec* 18:281-2, 1961

Paffenbarger, R. S., Jr., & others: The picture puzzle of the postpartum psychoses. *J. Chronic Dis* 13:161-73, 1961

. . .

## SUICIDE

Suicide is a major public health problem throughout the world and is one of the 10 leading causes of death in the United States. Early recognition of suicidal tendencies, careful evaluation of depressive tendencies, and prompt preventive measures are necessary if the suicide rate is to be reduced.

Depressed patients must always be regarded as potentially suicidal, but certain attitudes and responses of the patient may assist the doctor in determining the relative probability of suicide.

### Recognition of Suicidal Tendencies.

A. Elicit a history and search for physical evidence of previous attempts (e.g., wrist or neck scars, mouth or esophageal scarring and strictures from ingestion of corrosive poisons). Distinguish serious attempts which have failed from superficial gestures (benign attempts). Both are important since a superficial gesture may end in suicide by "mistake."

B. Expressions of Death Wishes or Suicidal Intentions. The discovery by the family of informal wills or bequests of property is a strong clue. One-third of suicides announce their intention. A patient who is "afraid" he may commit suicide is usually less likely to do so.

A patient who feels that he "deserves to die" or that "life holds no hope" is more liable to commit suicide, these patients may think of suicide but carefully conceal their intentions.

C. Evidences of mental depression of any type, unexplained fatigue and weakness, bizarre somatic delusions, apprehension, self-deprecation, self-accusation and a pathologic sense of guilt, lack of interest in family, work and friends, anorexia, weight loss, and constipation, insomnia, recent personal failure, grief, or tragedy, disappointment, especially in love affairs, and loss of self-esteem during adolescence, following divorce, or discovery of a spouse's infidelity.

D. Failure of Improvement. If a patient remains depressed in spite of a physician's help, the chances of suicide are increased. Caution must be observed since at times a lessening of the depression may indicate that the patient has made the decision to commit suicide, he has a feeling of relief since he knows his "problems will soon be over."

E. A patient who has withdrawn from routine living is a poor suicidal risk. The patient who, even with effort, continues his normal daily contacts and work is not so liable to be suicidal.

F. An increase in neurotic symptoms, which serve as defense mechanisms, usually indicates that the patient is not likely to commit suicide.

### Prevention of Suicide

Early detection of depression and prompt discussion with the patient's family are the urgent responsibilities of all physicians.

Prompt psychiatric consultation is indicated for all seriously depressed patients to evaluate the risk of suicide. Hospitalization is required for all severely depressed patients, so that psychotherapy, antidepressant drugs, and ECT can be given as indicated. The physician must also make every effort to prevent premature removal of potentially suicidal patients from the hospital. Repeated suicidal attempts are most apt to occur during the so-called recovery period, i.e., when depression has lessened because the patient has decided on suicide as the solution to his problem. Psychiatric observation and treatment of depressed patients should be continued after discharge from the hospital until the physician is satisfied that the danger of suicide no longer exists.

Do not give sedative or hypnotic drugs to depressed patients. They sometimes intensify

depression, or may be hoarded and used for suicidal purposes. If sedatives are necessary for sleep they should be dispensed by a member of the patient's family who retains custody of the supply.

- Pokorny, A D. Characteristics of 44 patients who subsequently committed suicide. *Arch Gen Psychiat* 2 314-23, 1960
- Schneidman, E S., & N L Farberow. *Clues to Suicide*. McGraw Hill, 1957
- Tuckman, J., & H E Connor. Attempted suicide in adolescents. *Am J Psychiat* 119 228-32, 1962
- Yessler, P G., & others. On the communication of suicidal ideas. *Arch Gen Psychiat* 3 612-31, 1960

## PERSONALITY & PERSONALITY TRAIT DISORDERS (CHARACTER DISORDERS)

Persons with character disorders have a life long history of behavioral inadequacy, which generally consists of poor judgment, impulsive or irrational behavior, and poor social compatibility. They usually have little anxiety about their actions. The principal types of character disorders are the inadequate personality, schizoid personality, cyclothymic personality, emotionally unstable personality, passive-aggressive personality, paranoid personality, and compulsive personality. (See p 470 for definitions.)

These persons usually seek help only when their personal inadequacies have gotten them into difficulties with others, e.g., their families, co-workers, or neighbors, and their reason for coming to a physician is to be extricated from their difficulties. They are frequently brought to the physician by the marital partner or a parent to be "changed."

In most personality trait disorders, supportive counseling and advice regarding specific difficulties are all that can be offered by the physician. Medications are of little or no value. Persuasion, guidance, and insight therapy are generally ineffective, but in selected cases where sufficient anxiety about behavior is present, some benefits may be derived from prolonged psychotherapy (especially psychoanalysis).

## PASSIVE AND AGGRESSIVE PERSONALITIES

The passive personality, the aggressive personality, and the passive-aggressive personality are among the more commonly encountered types of character disorder.

In childhood, over-protection or rejection (or alternations of both attitudes) tend to condition these individuals to the life-long expectation of being helped or cared for. Covertly, however, they resent and reject the protecting person. Passive-dependent types attach themselves to stronger persons (in marriage, at work, and in social contacts) but continue to react with unconscious anger toward the substitute parental figure and have deep feelings of inadequacy about themselves. Depression is a frequent symptom when they eventually discover that they have failed to fulfill themselves as mature persons.

The aggressive type protests most actively and openly against his need for security and often finds himself in conflict with authority figures (at school, at work, in marriage, and with society).

The passive aggressive type shows alternations or combinations of the 2 patterns of behavior.

Guidance and maintenance of firm boundaries to control acting-out tendencies are necessary for all of the character disorders, especially the passive and aggressive types. As in the case of the other character disorders, psychotherapy (especially psychoanalysis) is of some value when anxiety is present.

## THE COMPULSIVE PERSONALITY

The obsessive compulsive reactions as a specific psychiatric diagnosis (see p 477) should be distinguished from other types of compulsive behavior such as a compulsive need for neatness and order or compulsive eating, smoking, talking, drinking, or masturbation. Such individuals are more properly designated as compulsive personalities with anxiety. Anxiety is relieved by performing the compulsive act, but the anxiety is usually related to a specific situation about which the patient is aware. These acts are also more suitably related to the general situation in which they are performed and hence do not seem illogical to the patient, whereas in the obsessive compulsive reaction the thought or act is completely alien to whatever the patient is doing, thinking, or feeling at the time.

The compulsive personality may be subject to a wide variety of functional disorders. Certain diseases (e.g., migraine, idiopathic ulcerative colitis) occur with increased frequency in patients with compulsive personalities.

Treatment consists of simple psychotherapy designed to relieve anxiety. Tranquilizing medication and environmental changes are often useful.

### NONPSYCHOTIC PARANOID PERSONALITIES

Paranoid disorders range from simple paranoid personalities ("cranks," habitual litigants, espousers of various odd causes) to the truly psychotic paranoid personality (one of the subtypes of schizophrenia). It is important to distinguish between nonpsychotic and psychotic paranoids since the latter may act on their delusional beliefs and become dangerous to other persons. Nonpsychotic paranoid personalities frequently give a life-long history of sensitivity, fixed ideas, and dedication to unpopular causes. Suspicion may occur as a temporary response out of proportion to the extent of personal insult or rejection which the individual has actually endured.

In both the psychotic and nonpsychotic types, intelligence is preserved but logical thinking is based on illogical premises. The patient is oversensitive to the attitudes of others, and reacts with wounded pride, withdrawal, or sometimes with verbal assault to attempts to convince him that he has misinterpreted the facts.

The simple paranoid personality may, with some tolerance on the part of his associates, function quite harmlessly in society. Psychotic paranoid individuals should be evaluated by a psychiatrist. Hospitalization and treatment with tranquilizing drugs and ECT is effective in some cases.

Bullard, D. M. • Psychotherapy of paranoid patients. *Arch Gen Psychiat* 2:137-41, 1960

## SOCIOPATHIC PERSONALITY DISTURBANCES (PSYCHOPATHIC DISORDERS)

In general, patients with these disorders have basic feelings of insecurity and inadequacy and act out their feelings in asocial or antisocial patterns. Behavior is impulsive, without regard for the feelings or welfare of others, and the pattern usually begins in childhood and lasts throughout life, with disastrous consequences in marriage and interpersonal relationships and frequent encounters with law-enforcement agencies. Feelings of guilt are usually not present, and the patient often presents a surface glibness and deceptive facade which conceal his egocentric and narcissistic personality.

The potential sociopath is often an obstinate child who has frequent temper tantrums, tells lies with considerable facility, and may be cruel to animals and smaller children. Nailbiting, terror dreams, phobias, and maladjustment to group situations are characteristic traits. During adolescence he tends to show an inordinate interest in sexual matters, is shy, often in conflict with parental and community authority, and exhibits a variety of impulsive emotional reactions which are out of proportion to precipitating factors. Failure to identify with mature persons during early life (sometimes because of separation from or rejection by a parent) is thought to be an important etiologic factor. During adolescence there is a tendency to seek similarly lost or uncertain personalities and to establish ties and identifications with them. By adulthood, especially in a free society which offers a wide range of possible behavior, his narcissistic acting out becomes more damaging to others, with unhappy marriages, wild business schemes, sexual perversions, gambling, and attempts to anesthetize hurts, resentments, and loneliness with alcohol and addictive drugs.

It is well to remember that in some cases sociopathic behavior overlies a more basic psychosis or occurs as the result of brain damage. Psychometric and neurologic investigations, including EEG studies, are frequently of value.

Most sociopathic personalities respond poorly to formal psychotherapy. As a rule they seek help only when they are in difficulties with the law or when their egocentric needs are threatened. They then seek only extrication from their distress and tend to project their difficulties onto the outside world. Insight with feeling is difficult for them to attain.

In many circumstances the best that can be offered the sociopath is to provide structured situations with adequate disciplinary control in an attempt to limit the damage which he can do to himself or others: summer camps and special schools for young people; probation and legal restraints for the adult.

- Lipton, H. R.: The psychopath. *Arch. Crim. Psychodynamics* Special Issue 4:542-9, 1961.  
 O'Neal, P., & others: Parental deviance and the genesis of sociopathic personality. *Am. J. Psychiat.* 118:1114-24, 1962.  
 Raeburn, W., & others: Assessing the offender for the courts. *Brit. J. Crim.* 1:102-9, 1960

## SEXUAL DEVIATIONS

In the broadest sense, the sexual deviations and perversions include any type of sexual behavior which provides the individual with his major sexual gratification outside the normal act of coitus. Perverse acts, however, may accompany normal coitus, in which case they may be considered nonpathologic. Covert interest in the unusual aspects of sexuality is present to some degree in most persons.

Sexual deviations and perversions are found in both sexes, but are more common among men. Common types include overt homosexuality, pedophilia (sexual assault upon or activity with children), fetishism (sexual fixation on parts of the body, e.g., hair, or on an article of clothing, e.g., a shoe or corset), transvestitism (gratification gained through wearing the clothing of the opposite sex), exhibitionism, voyeurism (peeping Toms), and sadomasochism (gratification obtained through inflicting or experiencing pain).

Many degrees of deviation and perversion exist. For example, it is possible for an individual to marry and beget and rear children and also to carry on an active homosexual relationship outside of marriage. Other persons who would not ordinarily engage in homosexual activities may actively do so during periods of prolonged isolation from the opposite sex while in prison, remote military camps, or boarding schools. The extent to which such behavior may be considered pathologic depends greatly on the persistence, repetition, and nature of the physical contact beyond the pubertal years. Casual "crushes" on persons of the same sex are considered more or less normal during puberty or early adolescence.

Genital contact between persons of the same sex usually indicates that an emotional problem is present.

In all cases of sexual deviation and perversion a severe underlying psychic disturbance is present. The origin appears to be in childhood. Few cases, if any, are due to hormonal imbalance or anatomic defects.

### Sexual Perversion & the Law.

For legal reasons the physician must often distinguish 2 different categories of these disorders: Those which represent actual threats to other persons or to public welfare, and those which are merely distasteful or annoying or which arouse public anxiety. In the first group are those acts which are carried out in public places, are performed with or upon a minor, or which involve coercion or violence. In the latter group are included many acts of voyeurism or exhibitionism, which may be considered to have little more than annoyance value. The distinction is not always easy to make, however, since a child or impressionable person may be psychologically damaged by the act of an exhibitionist.

The physician called upon to evaluate problems involving sexual deviations must be aware that some minors may actually indicate readiness for or overtly invite acts of perversion by an adult. Under the law, however, the responsibility always rests upon the adult.

In many cases which involve two or more adults there is no clear evidence about which is the offender and which the victim, and willing participation on the part of both is the rule.

Many acts of perversion are carried out while under the influence of alcohol or other drugs, in which case the sexual problem may be complicated by the problem of addiction.

In recent years the law has changed its point of view with regard to many sex offenses, and the tendency now is to regard them as partially medical problems rather than purely legal ones. The establishment of psychiatric rehabilitation programs in state prisons and special treatment centers for sexual offenders represents efforts by society to help as well as isolate those whose sexual aberrations constitute a threat to the community.

### Treatment.

All perversions are most difficult to modify with any known form of treatment; the restraining actions of the law and community sanction remain the most effective deterrents. Treatment with hormones is generally futile.

Sexual deviates rarely seek help for their sexual problems since they do not wish to be deprived of opportunities for gratification.

They may be brought to the physician through external pressures (family or the courts), or they may seek psychiatric help for emotional problems which are peripheral to their sexual difficulty, e.g. jealousy, hostility or depression when jilted by a partner. Some help for these secondary emotional problems can and should be given, but basic change rarely is possible through psychotherapy.

With some adolescents who have only recently been introduced to perverse behavior, the prognosis is not entirely poor. Prolonged psychotherapy and counseling may be effective.

- Halleck S I Management of victims of sex offenders J A M A 180 273 8 1962  
 Kurland, M L Pedophilia erotica J Nerv & Ment Dis 131 394-403, 1960  
 Pacht, A R, & others Diagnosis and treatment of the sexual offender: a 9 year study Am J Psychiat 118 802 8, 1962

## ALCOHOLISM

### (Problem Drinking & Alcohol Addiction)

#### Essentials of Diagnosis

- Repetitive or chronic use of alcohol in any form to solve personal problems
- Continuing problems in any area of life which are related to the use of alcohol economic, social, family relationships, physical well-being or self deprecation
- Usually marked emotional difficulties such as depression, insecurity, feelings of inadequacy, and need for control over others
- Alcohol use, even in small quantity, allows expression of emotions otherwise repressed

#### General Considerations

Alcoholism is a syndrome consisting of 2 phases: problem drinking and alcohol addiction. Problem drinking is the chronic or repetitive use of alcohol to alleviate tension or help solve other emotional problems. Alcohol addiction is a true addiction similar to that which occurs following repeated use of narcotics. Problem drinking usually progresses to addiction. Both phases should be treated as part of a single illness which must be considered chronic and progressive as long as the use of alcohol continues.

The acute intoxicated state (drunkenness) and the postintoxicated state (hangover) may occur in either the problem drinker, the true alcohol addict or in any person who drinks a

sufficient amount of alcohol. Neither the problem drinker nor the alcohol addict can be diagnosed upon the basis of drunkenness alone since the drinking patterns and amounts consumed may be such that obvious drunkenness is not always attained. Until recently, most physicians have considered medical treatment to be appropriate only for the acute intoxicated state, hangover, specific complications of chronic use of alcohol such as delirium tremens, and for the many physical complications which result from chronic use, e.g., cirrhosis of the liver, cardiac disorders, neuropathies, and gastrointestinal ulcers. The current tendency, however, is to regard alcoholism as a disease entity, and many approaches to treatment have been devised.

The causes of alcoholism are varied, and include psychic, cultural and perhaps physiologic factors. Certain cultural groups (e.g., those of northern and central Europe and native American Indians) seem to be more prone to alcoholism than others. Proneness involves cultural factors rather than purely physiologic factors.

Most persons who develop a dependency upon alcohol have long-standing problems of anxiety, depression, and feelings of dissatisfaction with life and personal inadequacy. A few alcoholics have basic psychotic problems and use alcohol to alleviate the extreme panic which occurs when they fear an approaching loss of contact with reality.

Alcoholics are prone to transfer their dependency on alcohol to other substances, especially the tranquilizers, barbiturates, paraldehyde and amphetamine drugs. In these cases the combination of alcohol with these substances imposes an additional hazard to health.

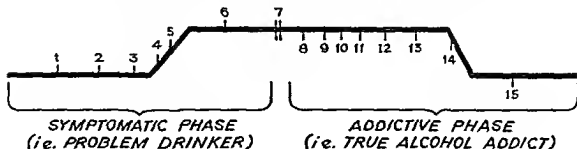
#### Diagnosis

The diagnosis of alcoholism is often missed by the physician since its protean manifestations must be sought in the often closely guarded emotional and adjustment areas of the patient's life and since the physical effects of persistent drinking do not become apparent until many years have passed. Physical examination of the problem drinker and the early alcohol addict usually reveals nothing abnormal.

The alcoholic person is naturally reluctant to talk about his reliance upon alcohol, and in many cases is not aware that he has a drinking problem. He may deny the extent or ways in which he uses alcohol when directly questioned. The spouse may tend to shield the patient from exposure, but in most cases the wife or husband is well aware of the difficulty and is deeply concerned about it.



# The Progression of Problem Drinking to Alcohol Addiction (Modified From Jellinek)



- 1 Increase in frequency of alcohol use
- 2 Begins to move in those groups where alcohol is part of "social communication"
- 3 Sneaking drinks
- 4 Gulping drinks
- 5 Increase in tolerance to alcohol needs more for same effect
- 6 Occurrence of blackouts, i.e., brief periods of amnesia while under influence of alcohol
- 7 Physiologic-psychologic change occurs. One drink leads to another. Compulsive need for alcohol. Changes in feelings occur after first drink leading to sensitivity about references to drinking, suspicions, resentments. This is a point of no return,

- 8 the ability to drink socially is never regained, and total and permanent abstinence are necessary
- 9 Drinking in the morning ("eye-openers")
- 10 Prolonged bouts of drinking ("binges")
- 11 Belligerent and grandiose behavior
- 12 Geographical cures, i.e., patient moves from town to town, changes jobs, marriages, living habits, in each case "swearing off" to start life all over in another pattern
- 13 Hiding and hoarding of alcohol supply
- 14 Paranoid ideas
- 15 Decrease in tolerance to alcohol
- 16 Physiologic changes with pathology in liver, cardiovascular system, central and peripheral neuropathies

Alcoholism affects both sexes. Most cases go unidentified for several years until one or more crises arise in the alcoholic's life. Overt evidence of alcoholism appears most commonly in the age group from 35-50. No economic, social, or racial group is immune, and it has been estimated that about 5.5 million persons in the United States are alcoholics. Fewer than 10% of alcoholics are on Skid Row, and the ratio of men to women in the United States is 5.5:1.

The form in which alcohol is used (beer, wine, distilled spirits, etc.) does not alter the ultimate diagnosis of alcoholism, nor does the frequency of use and the pattern of drinking. Some alcoholics drink daily, some only after a particular hour of the day, or on weekends, paydays, or on occasional binges. Some prefer to drink alone, or with friends in bars, others drink clandestinely, hiding the bottle from others in the family. Alcoholics who claim "social drinking only" can usually be shown, upon close inspection, to be drinking more than others in their social group.

## Treatment

No matter what form of treatment is used, the most practical goal for the alcoholic is total and permanent abstinence. Almost all aspects of his physical and emotional health depend upon achieving this goal. Neither total nor permanent abstinence may be expected for many alcoholics, but even partial gains are important since they help arrest the progression of alcoholism at least for awhile and help set the stage for more complete success at a later time.

The following general guides should be observed in treatment:

- (1) Use medications and hospitalization sparingly, and only when necessary to interrupt acute binge drinking, for hangover symptoms, severe depression, or other complications of alcohol overuse.
- (2) Treat medically all physical difficulties directly or indirectly related to alcoholism.
- (3) Provide the patient and his family with clear information regarding the diagnosis, nature, and prognosis of his illness.
- (4) Counseling should be provided for both the alcoholic and the wife or husband. It may

be given by a physician, clergyman, or psychiatrist, or by abstinent alcoholics. Sometimes a combination of counselors with different backgrounds is more useful than one counselor only, but all counselors must be of common opinion and must avoid confusing the patient with conflicting advice.

(5) Refer the alcoholic whenever possible to Alcoholics Anonymous (A A) and the spouse to Alanon (an organization for the relatives of alcoholics).

(6) Special medications such as disulfiram (Antabuse<sup>®</sup>) and special procedures such as conditioned reflex treatment will be beneficial for selected patients.

The kinds of treatment to be considered fall into the following 5 categories: (1) Medications, (2) psychiatric treatment or counseling for the alcoholic and the wife or husband, (3) Alcoholics Anonymous, (4) religious conversion or self-conversion, and (5) conditioned reflex treatment.

**A. Medical Treatment.** No medication is of specific value for the long-term or definitive treatment of alcoholism. At best, medications are of temporary or palliative value only and may help some patients over critical periods when their sobriety is threatened. (Caution: All patients who receive any type of medication should receive some form of regular counseling also.)

Medications for alcoholism may be considered under 3 general classes: (1) Sedatives, tranquilizers, and antidepressants, (2) antidipsotropics, i.e., disulfiram (Antabuse<sup>®</sup>); and (3) vitamin preparations, gastric sedatives, and antispasmodics.

**1. Sedatives, phenothiazine tranquilizers, and antidepressants.** - The main purpose of these medications is to act as substitutes for alcohol and to help relieve the anxiety or depression which precipitates drinking. Inasmuch as alcoholics will readily become habituated to almost any medication available to them, drugs should be given in minimal amounts and the frequency of dosage should be specifically prescribed. Because special dangers are present in the combination of many drugs, especially the barbiturates, with alcohol, the barbiturates should be used only with the greatest discretion and preferably not at all. Paraldehyde should not be used in the treatment of alcoholism (except in the management of delirium tremens) since its metabolism resembles that of alcohol so closely that giving it is comparable physiologically to offering the alcoholic another drink.

For the acute alcoholic episode, promazine hydrochloride (Sparine<sup>®</sup>), 50-100 mg. I.M.

stat., is effective in calming the disturbed and anxious patient and often removes the need for further binge drinking.

**2. Antidipsotropics - Disulfiram (Antabuse)** is often useful for those patients who recognize the need for total abstinence and who will accept self-imposed control. Administration by anyone other than the patient himself is rarely effective, and then only when the patient accepts the person who administers the drug as a helpful person rather than a controlling one. The effects of combining disulfiram with alcohol in minimal quantities are flushing, profuse sweating, precordial pain, marked palpitations, gastrointestinal spasms, and a feeling of impending death. These effects must be carefully explained to the patient before he makes his decision about whether to use the drug or not. The drug cannot be given unless the patient has been totally abstinent for at least 72 hours, and he cannot drink safely until 72 hours after taking it. The usual dosage is 1 Gm. daily for 4 days and 0.5 Gm. daily thereafter for at least the first month. The dosage may then be reduced to 0.25 Gm. daily for several months or until the patient feels secure in his abstinence.

A test of the effects of disulfiram when combined with alcohol is often useful in demonstrating to the patient what will happen if he drinks, but it is not necessary to perform such a test on a patient who is fully cooperative.

Patients with cardiac disease, severe liver damage, diabetes mellitus, and pulmonary disease should not be given disulfiram.

A variety of mild side-effects are reported by most patients, but few are serious enough to warrant discontinuation of the drug. Reported side-effects include dizziness, "bad taste in the mouth," gastrointestinal complaints, weakness, etc., and are generally believed to be the psychic results of withdrawal from alcohol rather than the physiologic effects of disulfiram.

All patients taking disulfiram should receive regular counseling.

**3. Gastric sedatives and antispasmodics** are valuable in alleviating hangover symptoms. The vitamins are important in correcting nutritional deficiencies. The medications selected and the methods of administration are similar to those used in the treatment of acute gastritis or for a malnourished patient.

**B. Psychiatric Treatment:** Almost all alcoholics need help with their emotional problems, and the relief obtained in psychotherapy increases the patient's chances of achieving abstinence. The most appropriate attitude for the physician is neither to condemn nor to condone the drinking. Frank discussion of the

patient's dependency on alcohol is important, and the physician may have to take the initiative in this since many alcoholics prefer to evade the issue of the importance of alcohol in their lives. Psychotherapy proceeds along the lines of constant support for all the patient's efforts to live without alcohol, helping him to recognize and understand his need for alcohol, and exposing the efforts he may make to blame his drinking on his wife, his parents, his employers, or on the need to seek relief because of "bad luck." The alcoholic will have difficulty in controlling his feelings of resentment, inadequacy, omnipotence, anxiety, and depression. The underlying character structure of the alcoholic is not predictable, but many of these people have had a negative self-image all their lives and will need considerable support during and after withdrawal of alcohol.

Abstinence is the ideal but not the only goal of therapy, nor is it attainable in many cases. Other goals of psychotherapy are lessening of anxiety and depression, increased feelings of confidence and adequacy, improved physical health through decreased drinking, a better social adjustment, and improved marital relations.

Even after total abstinence for many years many nondrinking alcoholics can profit from psychotherapy. Some of these persons occasionally experience periods of intense anxiety called "dry drunks." "Slips" are to be expected, even for the individual who is seriously attempting to attain total abstinence by any means. Slips must be realistically discussed and the patient dissuaded from self-recrimination about his failures.

Psychotherapy is usually most successful when the patient will also accept participation in Alcoholics Anonymous.

**Counseling or Psychotherapy for the Spouse:** The alcoholic tends to entice his wife and other pertinent persons (parents, close friend) or even society itself into playing special roles which perpetuate the drinking pattern. He particularly projects the role of persecutor on his wife, for example, and rationalizes his drinking as a weapon against her control. When convenient he may use her as his "rescuer," i.e., whenever he is in difficulty with others or feels depressed, helpless, or misunderstood. On other occasions he may maneuver her into the position of being a "dummy" or "easy mark": using lies, deceptions of all sorts, sneaking drinks, etc. Insofar as the wife, because of her own emotional needs, accepts the roles assigned to her she may contribute to the drinking problem. Abstinence is possible only when the spouse recognizes her own involvement and refuses to con-

tinue as a confederate in her husband's unconscious efforts to rationalize his behavior.

Common emotional problems among people married to alcoholics are anxiety, depression, immaturity, sexual difficulties, and passive or aggressive personalities. Even in those cases in which the alcoholic will not accept the diagnosis of alcoholism and refuses to seek help for his drinking, counseling of some sort is necessary for the spouse and may encourage the alcoholic in due time to seek help for himself.

**C. Alcoholics Anonymous:** Alcoholics Anonymous (A A) is probably the most widely known, the simplest, and the most practical method of attaining abstinence for most alcoholics. It is most effective when the patient also seeks some form of personal psychotherapy or counseling. Chapters exist in almost every city and close to almost every small community in the United States. The sincere desire to become abstinent is the only qualification necessary, and a phone call to another A A member is all that is required. Contact should be made by the drinker himself, but the physician may be most useful in introducing the idea to his patient and acting as liaison with an A A member who is willing to help.

A A is effective for several reasons: the spiritual nature of the organization, the understanding support of other alcoholics, the freedom to ventilate in the presence of other alcoholics, and the constant reminder through regular meetings that abstinence must be maintained on a daily or hourly basis.

**D. Religious Conversion or Self-conversion:** No reliable information is available about the number of alcoholics who have become abstinent without benefit of any formal or outside help. Undoubtedly many persons meet some crisis in their personal lives which serves to turn them away from alcohol ("swearing off"). Some of these take place as a "personal conversion" or spiritual transformation without benefit of religious persuasion. Others occur through the active intervention of a particular religious philosophy with or without a powerful emotional coloring. Various forms of conversion may occur, some with features resembling a kind of self-hypnosis, and may last for years or permanently.

**E. Conditioned Reflex Treatment:** Aversion therapy is sometimes successful in patients willing to accept this form of treatment. The procedure consists of the use of apomorphine or emetine to produce extreme nausea and vomiting at the moment of exposure (small

or ingestion) of alcohol. Periodic reinforcement is necessary until the reflex is firmly fixed or the patient is able to remain abstinent voluntarily.

**Alcoholics Anonymous** The Story of How Many Thousands of Men and Women Have Recovered From Alcoholism, 2nd ed. Alcoholics Anonymous 1955

Korman M., & others. Definition of alcoholism. J A M A 178 1184-6 1961

Ruprecht, A. L. The doctor's responsibility to an alcoholic. Postgrad Med 32 56-68 1962

## DELIRIUM TREMENS

Delirium tremens is an acute toxic psychosis which may develop in chronic alcoholics especially during and following a prolonged alcoholic episode. Both physiologic and psychic factors are involved. There is a long history of excessive drinking with prolonged binges. The delirium is usually preceded by restlessness, disturbed sleep and irritability following a recent binge. The symptoms include confusion and clouded consciousness often with epileptiform seizures, maniacal destructive behavior, and terrifying hallucinations frequently of distorted moving animals and figures.

The onset of the delirium may not occur for several days after drinking has ceased and there is some evidence that the drop in alcohol content in the body may be related to toxic effects.

Treatment is discussed on p. 489

Tavel, M. E. A new look at an old syndrome: delirium tremens. Arch Int Med 109 129 33 1962

## DRUG ADDICTION

Patients with personality disorders or emotional instability are particularly susceptible to drug addiction. Addiction to a wide variety of psychotropic drugs may occur, including opium and its derivatives, synthetic narcotic analgesics, tranquilizers, sedative and hypnotic drugs, and cortical stimulants (e.g., amphetamine). Addiction may follow the therapeutic administration of psychopharmacologic agents, and frequently occurs in neurotic patients who resort to their use in order to alleviate symptoms due to anxiety and ten-

sion. Sociopathic (psychopathic) patients, however, who utilize these drugs for their pleasurable intoxicant or stimulant effects, make up the largest percentage of addicts.

Addiction to any drug is characterized by a compelling need to continue taking it (addiction), often in increasing dosages (tolerance) and based upon a physiologic or psychic demand (dependence).

### Opium Derivatives & Synthetic Analgesics

A high degree of drug tolerance and dependence develops.

There are no characteristic symptoms or signs. Either somnolence or excitement may be evident. Emaciation, puncture marks and scars over the veins of the extremities, and miosis may be observed. In meperidine addiction there may be tremors, convulsions and dilated pupils. The intensity of withdrawal symptoms will vary with the addictive potential of the drug (most marked for heroin and least marked for codeine) and with the duration and degree of addiction.

Nalorphine (Nalline®) administration may rapidly induce characteristic withdrawal symptoms and is thus an aid in the diagnosis of questionable narcotic addiction or for periodic examination of former addicts to determine whether or not they have resumed the drug habit.

The withdrawal symptoms in morphine addiction are as follows:

- (1) First 24 hours: Drowsiness
- (2) Two to 3 days: Agitation, dilated pupils, muscle twitching, nausea, anorexia, vomiting, generalized muscular aches and pains, weight loss, insomnia, and increased temperature, pulse, respiration, and BP
- (3) Three to 12 days: Gradual decline of above symptoms
- (4) Three to 6 months: Nervousness, insomnia, and weakness

Treatment of addiction to narcotic drugs is best carried out in specialized institutions (e.g., U.S. Public Health Service Hospitals). In the United States the treatment of narcotic addiction must be carried out in conformity with the provisions of the Harrison Narcotic Act. Information regarding reporting and treatment of addicts should be obtained from the local office of the Federal Bureau of Narcotics.

Treatment consists of gradual withdrawal of narcotic drugs or substitution with methadone and gradual reduction of methadone dosage over a period of 15-30 days. Supportive measures, encouragement, and psychotherapy are usually necessary.

The prognosis for cure of narcotic addiction is unfortunately very poor except for those

few individuals who are highly motivated to overcome their addiction

#### Barbiturates & Other Sedatives.

*Psychophysiologic dependence occurs with these drugs but tolerance is not marked. The short-acting barbiturates (e.g., secobarbital, amobarbital, or pentobarbital) are most commonly employed in cases of addiction and may be taken in total daily doses of as high as 2 Gm. Symptoms of intoxication include confusion, slurred speech, yawning, somnolence, amnesia, ataxia, and hyporeflexia.*

*Withdrawal symptoms include restlessness, insomnia, tremors, convulsions (at times fatal), and acute brain syndrome.*

*Withdrawal treatment consists of cautious daily reduction of dosage over a period of 1-3 weeks. Psychotherapy must be directed at determining the cause of the psychiatric disorder.*

#### Amphetamine Drugs

*Little or no tolerance develops and there are no withdrawal reactions. These drugs are frequently taken in combination with alcohol and barbiturates and, to a lesser extent, the narcotic drugs. Symptoms include excitement, exhilaration, confusion, insomnia, anorexia, and increased muscular efficiency. Signs include tachycardia, dilated pupils, hypertension, and muscle tremors. Treatment consists of simple abstinence and psychotherapy for patients capable of developing insight.*

#### Marihuana

*No tolerance develops and there is no withdrawal reaction. The smoking of marihuana is largely limited to individuals with sociopathic personality disorders or maladjusted adolescents. The effect of smoking marihuana may often be due to the power of suggestion, but in large doses symptoms may include silly behavior, giggling, drooping of the eyelids, and delusions of time, place, and person. Alleged criminal behavior induced by marihuana is actually due to the underlying personality disorders of the users.*

*Treatment consists of simple abstinence and psychotherapy for selected patients capable of developing insight.*

Clark J A The prognosis in drug addiction  
J Ment Sc 108 411 8 1962

Expert Committee on Addiction Producing  
Drugs Twelfth Report WHO Tech Rep  
Ser 220 1962

## PSYCHOPHYSIOLOGIC DISORDERS (PSYCHOSOMATIC DISORDERS)

Commonly encountered psychosomatic disorders are as follows

(1) Circulatory system Essential hypertension, neurocirculatory asthenia, many arrhythmias

(2) Skin Neurodermatitis, alopecia, angioneurotic edema, urticaria, pruritus in erogenous zones

(3) Respiratory system Bronchial asthma

(4) Digestive tract Cardiospasm, anorexia nervosa, peptic ulcer, regional ileitis, mucous colitis, nonspecific ulcerative colitis, nervous vomiting

(5) Glandular (anterior pituitary, thyroid, pancreatic glands) Many cases of obesity as well as inability to gain weight

(6) Nervous system Migraine

(7) Genitourinary system Enuresis, vaginismus, frigidity and impotence

*Anxiety may in some persons be expressed by somatic fixation on any one of the visceral organs, as in many cases of peptic ulcer, essential hypertension, and neurodermatitis. Physiologic dysfunction and organic changes usually occur in the affected organ. Deep feelings of depression, rejection, anger, guilt, shame, power strivings, etc. usually accompany somatization.*

#### Differentiation of Organic & Psychosomatic Disorders From Conversion Reactions

Organic & Psychosomatic Disorders	Conversion Reactions
(1) Involvement of organs and viscera under autonomic nervous system control	(1) Involvement of parts under voluntary control
(2) Anxiety is not alleviated by the symptoms	(2) Anxiety is alleviated by the symptoms
(3) Symptoms primarily physiologic, e.g., essential hypertension, peptic ulcer	(3) Symptoms primarily symbolic, e.g., "paralysis"
(4) The physiologic changes may threaten life	(4) The symptoms do not threaten life

## THE PSYCHOTIC DISORDERS

Earlier investigation in the field of psychosomatic disorders suggested that specific types of personalities were more prone to develop specific types of physical illness. Thus essential hypertension has often been equated with the intense and driven type of personality, peptic ulcer with the worrier, bronchial asthma with the crying of the child, etc. These generalities have not been authenticated, and it is not yet known why certain persons select certain organs or systems for the somatic expression of their anxiety.

It is often difficult to determine to what degree physiologic changes are due directly to emotional factors and to what extent they are due to special habits and patterns in the patient's life, e.g., the dietary insult which often accompanies peptic ulcer.

## Treatment

Most patients with psychosomatic illnesses will need considerable help with their personal problems. Some may be suffering from specific anxieties which tend to intensify the illness even when they are not the direct and only cause of it. Others will need sweeping reorientation of their lives in order to reduce general stress as well as the specific feelings which have found expression through physiologic dysfunction. All medical efforts are directed toward symptomatic relief, and all psychiatric efforts must be aimed at removing psychogenic factors. Although psychotherapy may be of considerable value, it will not effect physiologic changes.

- Holt, H., & C. Winick. Group psychotherapy with obese women. *Arch Gen Psychiat* 5:156-63, 1961.
- Masserman, J. H. The office therapy of psychosomatic disorders. *Arch Gen Psychiat* 3:320-9, 1950.
- Rosenberg, J. A., Jr. The role of psychogenic factors in skin diseases. *Arch Dermat & Syph* 81:81-6, 1960.
- Wahl, C. W. Psychodynamics of the allergic patients. *Ann Allergy* 18:1138-43, 1960.
- Wall, J. H. Diagnosis, treatment and results in anorexia nervosa. *Am J Psychiat* 115:997-1001, 1959.

The psychoses may be classified as those of apparently psychogenic origin and those due to toxic or organic causes. The former consist of involutional psychosis (involutional melancholia), manic-depressive psychosis, psychotic depression, and schizophrenia.

The principal difference between the psychoneurotic disorders and the psychoses is that in the former the personality remains essentially intact, whereas in the psychotic disorders an almost total personality change occurs. The differences are qualitative rather than quantitative, and some of the psychoneuroses may be more severe and may have a poorer prognosis than some psychoses.

It has been said that the neurotic builds a house of fantasy but continues to live in the real world, whereas the psychotic withdraws from reality and lives in his house of fantasy. The psychotic patient, probably because of the anxiety he experiences in his private house, constructs his own laws of relating to people and interpreting his world.

Personality transformation in the psychoses occurs in 3 areas: (1) A predominantly symbolic transformation, in which the patient communicates by means of words and concepts which are apparently unrelated to his true feelings but in fact are substitutes for them - as in schizophrenia; (2) a predominantly affective transformation, in which the patient responds to internal stress with exaggerated mood changes - as in the psychotic depressions and manic-depressive psychoses; and (3) a predominantly cognitive transformation, in which the patient loses the ability to recognize and identify familiar objects and people - as in the psychoses due to toxic and organic causes.

A variety of physical and physiologic changes have been described in some of the psychoses (e.g., in the blood, urine, brain, and skin), but at this stage of medical knowledge it is not known to what extent these changes are clues to etiology or are the result of the psychotic's altered way of life.

The principal forms of therapy currently available for the treatment of the psychoses are as follows: (1) Electroconvulsive (ECT, ESI) and insulin shock therapy; (2) hydrotherapies and physical therapies during periods of acute disturbance; (3) psychopharmacologic agents, especially tranquilizing and antidepressant medications which help the patient become more amenable to psychotherapy; (4) re-education programs, including occupational therapy, socialization, music therapy, work therapy, and various guided or sheltered reorientation programs.

Some unique forms of individual and group psychotherapy have been reported, but their success depends largely on the selection of patients and the personality of the therapist. Psychosurgery is not generally used.

### Electroconvulsive Therapy (ECT)

This type of treatment consists of producing a convulsive seizure by means of a small controlled electric current through electrodes placed on the patient's temples. ECT is used for many types of depression and for some types of schizophrenia.

The number of convulsive seizures given and the intervals between shocks vary considerably depending upon the nature of the psychiatric illness and certain other factors such as the patient's physical condition and previous response to ECT. It is not known precisely why convulsive therapy works, but the therapeutic value resides in the convulsion itself rather than in the electric current. Theories of its value range from explanations based on purely organic reasoning to purely psychologic ones. For example, it has been argued that the convulsion may cause chemical changes in the brain cells, that it may help to muster all of the vital forces of the patient for survival, or that it may fulfill the patient's fantasies of death and rebirth. Inasmuch as all patients experience temporary loss of memory following ECT, it is also possible that the memory loss may be a major factor in improvement.

The main purpose of ECT is to restore the patient's contact with reality. In all cases, follow-up psychotherapy is indispensable.

This type of treatment should be given by a psychiatrist skilled in the procedure. A hospital setting is best but is not mandatory.

### A Types of Psychiatric Illnesses Which Respond to ECT

1 **Involuntarily melancholia** (all moderately severe and severe cases) - ECT is especially effective for these patients and is the treatment of choice. Improvement usually occurs after 4-6 applications given at intervals of a few days. Up to 12-20 applications are usually given to ensure improvement. Patients whose depressions have a paranoid component do not respond as well as others.

2 **Manic depressive psychosis** - ECT may be used for both the depressed and the manic phase. Four to 6 applications usually produce a return to normal mood and better contact with reality. Twelve to 20 further applications are given to sustain improvement. During an acute manic episode daily applications may be necessary.

3 **Postpartum psychosis** - Twelve to 20 applications generally produce marked improvement except when schizophrenic elements are present and especially if there is a history of benign schizophrenic symptoms.

4 **Senile depression** - A few applications are frequently successful and should be given in almost all cases of severe senile depression unless significant organic brain changes are quite evident.

5 **Psychotic depression** - ECT is the treatment of choice. Usually 12-20 applications are necessary. Follow-up ECT may be necessary to sustain the patient's contact with reality.

6 **Severe psychoneurotic depression** - Patients with or without agitation who do not respond to drugs and psychotherapy should be seriously considered for ECT. No precise rules can be laid down for the selection of these patients, but the current tendency is to defer ECT for neurotic types of depression in patients who have shown some response, no matter how slight, to any other kind of treatment. The following should be considered:

a Length of time in psychotherapy and whether or not any improvement has occurred.

b Whether or not a favorable response has occurred with antidepressant drugs or other medication.

c Whether or not environmental manipulation changes in work or residence, vacations or changes in the attitudes of people in the immediate environment have been effective.

d How long the patient has been completely unable to continue his usual occupation or how long he has shown complete lack of interest in his environment or in prescribed forms of activity (occupational and recreational therapies).

7 **Many types of schizophrenia** - ECT is generally useful for most of the acutely disturbed periods of this illness. The catatonic schizophrenic generally responds quite well, but the other types of schizophrenia are less amenable to ECT. Simple and hebephrenic types of schizophrenia tend to respond poorly. Up to 30-40 applications (over a period of weeks or months) are commonly used.

B **Psychiatric Contraindications to ECT** - ECT is not indicated for psychiatric illnesses other than those listed above. It should not be used for the psychoneuroses other than prolonged severe depression which does not respond to psychotherapy and medication, nor for the sociopathic and personality disorders, psychophysiological disorders, and addictions.

C **Safety of ECT** - Patients with coronary disease and severe cardiac decompensation

for whom ECT is contemplated must be carefully evaluated with due consideration for the risks of treatment as opposed to the necessity for treatment. In general however most of the medical conditions previously believed to be contraindications to ECT have been found to respond with complete safety to this form of therapy. Examples are as follows:

- 1 Old age ECT may be given safely to elderly and senile persons
- 2 Hypertension There is now general agreement that hypertensives react well to ECT and that the treatment may be effective in lowering BP
- 3 Pulmonary tuberculosis No contraindications to ECT
- 4 Pregnancy ECT may be given practically up to full term without causing rupture of membranes, uterine contractions or injury to the fetus
- 5 Peptic ulcer with a history of bleeding No contraindication to ECT, especially when the patient is properly prepared with muscle relaxants
- 6 Compensated nonacute cardiovascular disease No contraindication to ECT
- 7 Patients with a history of recent fracture or with bone disease may be given ECT when properly prepared with muscle relaxants

**D Mishaps Due to ECT** Accidents are uncommon with proper selection of patients and appropriate premedication (usually one of the barbiturates and muscle relaxants). Those accidents which do occur are usually fractures or dislocations of the lower and middle spine or the upper extremities (including the clavicle) and sometimes the mandible. Other complications are rare.

In all cases ECT causes a temporary complete loss of memory (in all spheres both recent and remote events) which may last for several weeks. Memory gradually returns however and there is no impairment of intellectual ability. During follow up psychotherapy it is frequently necessary to reassure the patient that memory will return intact.

Kallnowsky L B Some problems in electric convulsive therapy of depressions. In Depression P H Hock and J Zubin Grune & Stratton 1954

Rohde P & W Sargent Treatment of schizophrenia in a general hospital Brit M J 5244 67 70 July 8 1961

### Insulin Therapy

Insulin therapy may be given in 2 forms in subcoma doses or in full doses to achieve coma (insulin shock). Neither type is in wide use at the present time in the U S A since the psychopharmacologic agents and ECT are of such broad value. Subcoma insulin continues to be used at some psychiatric centers however in the treatment of prolonged acute anxiety in inadequate personalities. The use of insulin shock is considered to be of value for some of the psychoses which do not respond to ECT and drugs. In the latter cases insulin shock is usually given in conjunction with ECT as a combined treatment.

### Detention & Commitment of Disturbed Persons

Detention of emotionally disturbed persons even for an hour must have legal sanction. In actual practice most law enforcement officers upon a physician's request will detain persons who seem to be intoxicated, drugged, seriously confused, suicidal, homicidal or otherwise mentally ill pending possible commitment procedure. The usual procedure for commitment in most states of the U S A is as follows:

(1) A member of the patient's immediate family requests the district attorney (or comparable legal officer) to initiate commitment procedures. The family attorney may be called upon to assist with the arrangements. A physician's written opinion that the patient is disturbed and needs hospitalization usually accompanies this request. A public health commitment may also be sought in special circumstances upon the request of 2 physicians.

(2) Law enforcement officers escort the patient to a hospital where psychiatric evaluation and recommendations are made within a few days.

(3) A judge rules on the mental competency of the patient and the advisability of commitment, basing his decision on the recommendations submitted by the hospital psychiatrist and psychologists. The patient may demand a jury sanity trial at this point.

(4) The patient's civil rights are suspended if he is judged incompetent.

(5) The court may appoint a guardian of the patient's person of his property only or of both.

(6) Upon release from the hospital the patient may petition for restitution of his civil rights and release from guardianship.

Commitment procedures should be initiated by the family and not by the physician lest the patient or his family later seek legal action against the physician. Only after commitment is initiated may the physician safely offer his



professional opinion regarding the mental and emotional condition of the patient

He should retain notes of his examination for future reference

## INVOLUTIONAL PSYCHOTIC REACTION (Involuntional Melancholia)

### Essentials of Diagnosis

- Onset between ages 40-65
- Withdrawal of interest in environment, including interest in people, work, food, and sex
- Sleep disturbances, particularly difficulty in falling asleep and early awakening
- Unusual somatic concern with feelings of worthlessness and failure
- Considerable agitation is usually present

The involuntional psychotic reaction may sometimes be confused with manic depressive psychosis or with an acute schizophrenic reaction. The premorbid personality of the involuntional melancholic, however, will help in making the distinction. A history of disturbed behavior is generally present in the patient who develops a manic depressive or schizophrenic type disorder in this age group.

### General Considerations

The involuntional psychotic reaction is a severe depression with psychotic features which occurs during or after the climacteric in both men and women, although women are more frequently affected. In earlier stages of this depression the psychotic features may be minimal or entirely lacking.

During and following the climacteric many persons are unable to recognize and accept the inevitable decline in their physical, sexual, and working abilities and the fact that they can no longer compete successfully with younger and stronger persons. The degree of depression which may occur and the extent of associated mental mood and behavioral changes vary considerably. Without treatment this type of depression tends to run a chronic worsening course, and suicide is a constant risk. Medical intervention of some sort is always indicated.

The premorbid personality: The typical person who develops involuntional melancholia is the overly-conscientious, compulsive per-

son who feels he has sought little for himself, tending to devote his efforts to others (family, employees, society at large) whose acceptance he has unconsciously sought. During the climacteric such a person may come to feel he has deluded himself and wasted his energies, and that his chances for personal fulfillment are now lost. Such a patient may be deeply angry at himself for thus failing to realize his earlier ambitions. Precipitating factors are not always evident but may sometimes be obvious, e.g. the marriage of a son or daughter, reduction of income, or enforced retirement.

### Clinical Findings

Depression is usually intense, and is marked by considerable anxiety and agitation. Profound sleep disturbances and loss of appetite and weight occur. Sexual interest is reduced or absent, often to the point of impotence or frigidity. Somatic concern is common, sometimes with delusional paranoid ideas regarding certain organs or parts of the body. Vasomotor instability characterized by hot flushes, sweats, headaches and general apathy is a prominent feature.

Frenzied activity with vicarious aggressions, including unusual sexual interests and behavior, sometimes results and represents attempts to deny or fight against the curtailment of abilities.

### Treatment

**A Mild Cases.** Mild cases may be treated at home or in a nursing home if adequate and constant supervision is possible. Treatment may begin with complete bed rest for a few weeks. The patient's diet should be corrected, and insomnia treated symptomatically with barbiturates. Small doses of insulin are sometimes useful to encourage appetite. Tonics and vitamins are generally of no value, and forced (tube) feeding may be necessary. Simple reassurance and persuasion may be of the greatest value. Endocrine therapy may produce dramatic results, especially when the predominant symptoms are those of vasomotor instability. In most cases, however, the psychosis is based on factors more complicated than endocrine deficiency.

**B Severe Cases.** For more acutely disturbed patients, i.e., those in whom agitation and paranoid or suicidal tendencies are present, hospitalization is mandatory. Antidepressant medications are not generally useful, and the patient is inaccessible to verbal psychotherapy. ECT is the most effective treatment, and the results are usually dramatic.

**C Follow-up Treatment Psychotherapy** is indicated after ECT. The objective is to guide the patient toward insights which will enable him to adjust on a realistic level, to prevent the development of the egocentric, bigoted attitudes which some patients cling to in an attempt to bolster their self-esteem, and to prevent the patient from sinking into an attitude of apathy, feelings of inferiority, and defeat.

The patient should be urged to develop new and creative interests which involve friendly association with other people especially children and persons in his own age group.

## MANIC-DEPRESSIVE PSYCHOSIS

### Essentials of Diagnosis

- Occurs most frequently in young adults, two thirds are women
- Marked mood swings with phases either of increased psychomotor activity (mania) or decreased psychomotor activity (depression), or alternations or combinations of both
- Phases are extremely variable in severity, duration, and frequency
- Impairment of intellectual capacities is usually not evident during remissions

Differentiation from the catatonic type of schizophrenia or simple schizophrenia with secondary depression is not always easy in markedly depressed patients, but the absence of bizarre behavior and paranoid ideation is useful in making the differentiation.

### General Considerations

Although the term manic-depressive psychosis is most often used to signify psychotic states in which depression or elation and excitement are present, less pronounced forms of manic-depressive illness are quite common. The depression may be precipitated by real or symbolic circumstances which suggest loss to the patient. Most of these persons have cyclothymic personalities and have tended to respond throughout life with exaggerated mood swings. There is some evidence that hereditary, familial, and cultural factors may predispose to this disorder.

The manic-depressive person has an image of himself which varies from positive to negative extremes. During the depressed period he feels worthless and full of self-blame. During the manic phase his feelings are those of omnipotence.

### Clinical Findings

Almost any combination of the manic and depressive phases may occur. In atypical cases, manic and depressive features may be present simultaneously (e.g., agitated depression).

**A Depressed Phase** Along with other signs of depression there are characteristically a number of physiologic components: dry mouth, constipation, and sometimes blurring of vision. Appetite is poor, with concomitant weight loss, during the depressed period. The patient frequently complains that he would like to cry but is often not able to do so. Somatic complaints referable to the head and abdomen are quite common.

In almost all cases psychomotor retardation is present, the patient sits quietly, incapable of reacting to his environment, from which he may feel estranged.

One or more attacks may be experienced throughout the patient's life, with a tendency for recurrence of minor or major attacks. To a considerable extent the depressed period (as well as the elated period) is self-limiting after a period of several months. Suicide is a serious possibility during the depressed state, and most manic-depressive patients should be in a hospital under psychiatric supervision during either of the extreme periods.

**B Manic Phase** The manic phase is characterized by an extreme increase in psychomotor activity, with rapidity of speech, flights of ideas, silly behavior, distractibility, excitement, and meaningless physical movements (e.g., restless pacing, running, jumping, hitting walls, pounding doors, howling, tearing up clothing, and breaking furniture). In milder cases (hypomania) the patient is not disoriented, psychomotor activity is less marked, and there is no clouding of consciousness. In so-called acute mania the psychomotor activity is so marked that extreme physical exhaustion results, disorientation occurs, and consciousness is almost completely lacking.

### Treatment

These patients should be under the care of a psychiatrist. Hospitalization is necessary for the treatment of acute episodes in order to protect the patient as well as others. ECT is effective in shortening the depressed phase as well as the manic phase, although its effect on the ultimate prognosis of manic-depressive psychosis is questionable.

Good nursing care is essential. Tube feeding may be necessary.

Psychotherapy after acute episodes may be used as an adjunct to ECT.

The antidepressant drugs have been of value in the treatment of some of the psychotic depressive reactions, but their long-range effectiveness and toxicity remain uncertain.

Treatment of the manic phase is directed toward protecting the patient as well as others. Sedative-hypnotic and tranquilizing drugs may be administered orally or parenterally to control physical agitation. ECT is often necessary to control severely excited and elated phases of this illness.

#### Prognosis

The course is highly variable. Acute episodes may vary in duration from a few days to many years. Recovery from single episodes usually occurs, with or without treatment, although recurrences may be expected in about 50% of cases. If the onset is in early life, the prognosis is less favorable.

Arieti, S. Manic depressive psychosis. In *American Handbook of Psychiatry* Vol 1. Basic Books, 1959.

Gibson, R W, & others. On the dynamics of the manic-depressive personality. *Am J Psychiat* 115:1101-7, 1959.

### PSYCHOTIC DEPRESSIVE REACTION

The psychotic depressive reactions are severe depressions in which contact with reality is lost and total withdrawal into a delusional state occurs. The illness resembles the depressed phase of manic-depressive psychosis except that it may occur at any age.

The clinical findings of psychotic depression include intractable insomnia, delusions and hallucinations in which parts of the body may be conceived as dead, rotting, or alien to the patient, and severe depression with refusal to take food and ruminations about suicide. In some cases of psychotic depression the general psychomotor retardation is combined with severe agitation.

Psychotic depression is sometimes difficult to differentiate from neurotic (reactive) depressions, manic-depressive psychosis, and involutional psychosis. In reactive depression contact with reality is not lost and there are no hypochondriacal characteristics, no delusions or hallucinations, and no severe psychomotor retardation. In manic-depressive psychosis the life history usually shows mood swings or alternations. In involutional psychosis the clinical findings may be quite similar, but the latter occurs only in the middle or later years of life.

Treatment should be by a psychiatrist and is similar to that for manic-depressive psychosis and involutional melancholia - especially the use of ECT.

After the acute psychotic symptoms have subsided following ECT, psychotherapy, with guidance and direction in reorienting the patient's life, is usually necessary.

### SCHIZOPHRENIC REACTIONS (Schizophrenia, Formerly Known as Dementia Praecox)

#### Essentials of Diagnosis

- Usually a slowly progressive (but may be rapid) withdrawal from reality
- Inappropriate responses in thinking, speech and behavior
- Alternations of mood - flat, euphoric, withdrawn, or depressed - without apparent relationship to circumstances
- Speech and behavior become irrelevant (circumstantial) or irrational and delusional

#### Frequent Additional Signs

- Depersonalization in which the patient behaves as if he were a detached observer of his own actions, is a common finding
- Delusions of grandeur or persecution are often present
- Religious or sexual preoccupations are common
- Logical reasoning becomes impossible
- Flights of ideas and incoherence take the place of thought
- Mentation and speech become blocked in emotionally charged situations
- Auditory hallucinations, stereotyped activity, and ritualistic behavior are common
- Disturbances of consciousness, memory, and orientation are often present

#### General Considerations

Schizophrenia in any of its forms is one of the most common types of emotional disorder. Over 50% of mental hospital beds are occupied by patients with this illness. The onset may be at any age, but usually occurs during late adolescence and early adulthood. Schizophrenia is characterized by severe disruption in the usual logical connection of thoughts. The patient's thoughts are dissociated from his feelings, and a separation thus occurs between the patient and reality. Mood

and behavioral changes occur, and various degrees of disintegration of the personality. Some authorities maintain that this illness is a syndrome or group of disorders ("the schizophrenias"). All patients in the "group," however, have certain common characteristics which would seem to justify classifying them together as suffering from a common entity called the schizophrenic reaction.

Four main types have been described. All types seem to be essentially one and the same illness, and considerable fluidity between types occurs.

(1) **Simple type** Characterized by a gradual withdrawal from reality, apathy, inappropriate moods and behavior, irritability out of proportion to the stress, and slow mental and intellectual deterioration. Delusions and hallucinations are rare.

(2) **Paranoid type** Suspiciousness rapidly progresses to active auditory and visual hallucinations of a persecutory nature. The delusions frequently involve electricity, machinery, TV, atomic energy, etc., with elaborate rationalizations by the patient. Food may be refused on the grounds that it is poisoned. Acts of violence and murder may be carried out against those suspected of persecuting the patient.

(3) **Catatonic type** Fluctuating episodes of stupor and excitement occur. During the stuporous or negative phase the patient may assume bizarre body postures, including that of wax flexibility, or may stare for hours into space listening to condemnatory or commanding voices. The delusion of being God or Christ or having supernatural powers is not uncommon.

(4) **Hebephrenic type** Bizarre mannerisms, incoherent speech and silly and grotesque behavior with hysterical laughing and crying may be present. There is some evidence that the hebephrenic type is a further deterioration of the paranoid type, and it is less common now that enlightened hospital care has tended to keep deterioration to a minimum.

There is some evidence that any of the 4 types may be expressed clinically in either of the 2 following ways: reactive schizophrenia, in which the patient's illness is his unique response to extraordinary stress and which tends to be short-lived or recurrent, with periods of relatively adequate adjustment between reactions, and "process" or malignant schizophrenia, which begins fairly early in life, follows a more chronic course, and becomes a distinct way of life. In the latter type prolonged hospitalization is often necessary.

## Etiology.

The causes of the schizophrenic reaction are still unclear and are probably multiple. A genetic potential or susceptibility may exist; frustrations and deprivations, especially those which occur during the first year of life, seem crucial; later childhood conditioning (e.g., rejection through separation of the parents) augments a tendency to "turn inward"; later environmental factors, usually resulting in poor personal relationships, may propel a predisposed individual into a schizophrenic type of reaction.

## Onset & Course

**A Acute Onset:** The schizophrenic reaction may manifest itself at any age as a sudden break with reality. Excitement, inappropriate affect, irrelevant babbling and weird gesturing, and suicidal, homicidal, or maniacal behavior may be present. The duration may be relatively brief (if prompt treatment is given), or the disease may progress to a chronic or recurrent form.

**B Benign Onset:** Slowly progressive deterioration, usually during late adolescence or early adulthood, is more common than acute onset. Inasmuch as premorbid signs are usually evident, it is important that the physician be able to recognize the harbingers of the schizophrenic break with reality. The "odd" individual who is out of harmony with himself and the world is most suspect. The brooding post-adolescent, persons who indulge types of thinking which involve an unusual fantasy life, sexual preoccupation, philosophic speculations and quests for the mystical or absolute, the antisocial, critical, stubborn, and inflexible person who finds no direct satisfaction in life—all are predisposed to this disorder.

## Treatment

Treatment depends upon the stage of the illness, the depth of regression, the degree of grasp upon reality that remains, the motivation of the patient for treatment, the response to medication and ECT, and the ability of the patient to establish a relationship with a therapist.

**A Less Severe Cases:** Mild forms of this psychosis which seem to be precipitated by overwhelming external stress may sometimes be treated by environmental manipulation. At best, changes in the external circumstances of the patient's life can be helpful in returning him to his prepsychotic level of adjustment. Tranquilizing medication is indicated, often in massive doses if anxiety is intense. Among

the more useful psychopharmacologic agents are the phenothiazines and meprobamate. Trifluoperazine (Stelazine®) (up to 20 mg /day) is particularly recommended for the more withdrawn type of patient, and chlorpromazine (up to 600 mg /day) for those with agitated features.

Many "recovered" schizophrenics will have occasional recurrences of mild psychotic symptoms in response to stress. For these patients supportive psychotherapy with tranquilizing medications tends to prevent the illness from becoming more severe.

In all milder forms of schizophrenia some type of continued relationship therapy is indicated. Psychotherapy takes the form of simple reality testing, reassurance, guidance, and insights within the limits of the patient's ability to understand his feelings and the meaning of his symptoms. Anxiety must be kept to a minimum, and a positive relationship with the therapist must be maintained.

Depending upon the patient's ability to form emotional ties with objects or persons outside himself, therapy may be through individual or group sessions. Verbal, occupational, and activity forms of therapy may be used, and should be carried out by persons who are skilled in working with such patients.

The encouragement of compulsory routines of work and daily living is necessary and will enable many patients to overcome some of their personality defect.

**B Severe Acute Cases:** Acute and severely disturbed schizophrenic reactions call for immediate hospital care. Hydrotherapy (continuous tubs, cold packs) and the use of sedation, often by parenteral routes, are indicated. The barbiturates and certain of the phenothiazines may be used, as well as chloral hydrate orally or I.M.

ECT is strongly indicated for most of the acutely disturbed forms of the disease no matter whether the predominant symptoms are those of excitement or withdrawal, and is the most suitable type of treatment for all acute stages of this illness.

**C Treatment During Partial Remission:** Well-supervised self-care programs of work and play are necessary. Re-educative procedures of all kinds are best undertaken in a hospital setting along with individual and group forms of psychotherapy.

**D. Chronic Forms of Schizophrenia:** The majority of psychiatric hospital beds in this country are occupied by patients with chronic schizophrenia, which is the end result of personality deterioration. Many of these patients,

depending upon the quality of hospital treatment, are capable of partial readjustment in a closely structured situation in the hospital or in foster homes. ECT during periods of overt psychotic disturbance or withdrawal and the judicious use of psychopharmacologic agents, along with routine physical evaluation and daily life supervision, are indicated. Individual and group psychotherapy are also useful in maintaining reasonable adaptation and preventing further regression.

**E Psychotherapy With Schizophrenic Patients.** Aside from the supportive forms of psychotherapy a variety of unique forms of symbolic, analytic, interpretative, and directive psychotherapy have been described (e.g., by John Rosen, Frieda Fromm-Reichman). The results obtained seem to be due to careful selection of patients and the individualized techniques and personality of the therapist. There is no doubt that all patients who have benefited from these forms of psychotherapy have received the benefit of extensive and highly personalized relationships with the therapist during frequent long sessions for many months or years.

### Prognosis

The course in the benign type is variable. Some patients recover fairly promptly and are able to return to their premorbid level of adjustment. Many cases "heal with scarring of the personality" so that, despite their recovery, they still give the impression of being odd persons. Others progress to a more or less chronic course, with enlightened hospital treatment, they have less tendency now than formerly to deteriorate to such a degree that they cannot take care of such basic needs as feeding and dressing themselves.

Many acutely disturbed patients recover readily and, with follow-up psychotherapeutic help, are able to readjust adequately although the possibility of recurrences remains.

Arieti, S.: Psychotherapy of schizophrenia. Arch. Gen. Psychiat. 6:112-22, 1962.

Bateson, G., & others: Towards a theory of schizophrenia. Behavioral Sc. 1:251-64, 1956.

Ferreira, A.J.: The etiology of schizophrenia: a review. California Med. 94:369-77, 1961.

Freeman, T.: A psycho-analytic approach to the diagnosis of schizophrenic reaction. J. Ment. Sc. 108:286-99, 1962.

## BRAIN SYNDROMES

### ACUTE BRAIN SYNDROME

#### Essentials of Diagnosis

- Usually acute but at times insidious onset of disturbance of perception and interpretation of stimuli (delirium)
- Confusion disorientation agitation excitement
- Hallucinations delusions anxiety and fear

The differential diagnosis of acute brain syndromes is mainly that of identification of the various primary etiologic factors. At times an acute brain syndrome must be distinguished from schizophrenia but the history of head injury cerebral or meningeal infection or evidence of drug or alcoholic intake is usually sufficient to make the distinction.

#### General Considerations

Acute brain syndrome is the term given to a group of disorders of perception and interpretation associated with delirium. The causes are varied and include intoxication with drugs (e.g., bromides, barbiturates, alcohol, atropine, corticosteroids), metabolic diseases (e.g., uremia, thyroid crises, diabetic acidosis), pellagra, dehydration, systemic infection with high fever, intracranial infections, and head injury. More than a single etiologic factor may be in operation at the same time.

#### Clinical Findings

**A Symptoms and Signs.** The principal clinical findings in acute brain syndromes are confusion, disorientation, and delirium. Close questioning of friends, nurses, or relatives will often reveal that there has been an insidious onset of restlessness and anxiety and that the patient has shown an increasingly more suspicious attitude toward others. These symptoms are often more severe at night. Without treatment these symptoms will progress to extreme confusion, disorientation, hallucinations (mainly visual), marked restlessness and excitement, and defects in memory and retention. The severity of symptoms fluctuates markedly. In extreme cases there may even be sudden attempts at homicide or suicide.

The clinical findings of the primary disease may also be present (e.g., dilated pupils and dry mouth in atropine intoxication; respiratory depression in barbiturate toxicity; abnormal neurologic findings due to brain injury).

**B Laboratory Findings.** Laboratory findings are important in determining the etiology of the delirium, e.g., elevated blood bromide or alcohol levels, urinary barbiturate levels, and BUN.

#### Treatment

**A Protect From Physical Injury.** Use the safest room available, preferably on the lowest floor of the building. Windows should be covered with locked heavy screens if possible. Remove all furnishings from the room except a low bed with side boards or, if necessary, simply a mattress on the floor. The room must be free of sharp objects and glass. Avoid mechanical restraints whenever possible, except for specific medical or surgical reasons. Use "chemical" restraints or hydrotherapy (see below). Caution: Observe for suicidal or destructive tendencies.

**B Reassure the Patient.** Be kindly and understanding. Recognize the patient's sensations as those of a confused and sick person. See that the room is adequately lighted both day and night and free from shadows. Unusual noises should be avoided, but familiar sounds may actually reassure the patient. Remember that the patient may be confused and will misinterpret strange sensory stimuli. Help the patient to understand what is happening and why he is in his particular situation. Do not misrepresent the facts. Explain diagnostic and therapeutic procedures when necessary.

Recruit the aid of the patient's relatives and friends, since, as familiar figures, they may allay his apprehension. However, some patients frequently become disturbed under these circumstances.

Constant nursing attendance is necessary.

**C Sedative and Hypnotic Drugs.** Tranquilizers (See tables on pp. 502 and 503).

1. Promazine hydrochloride (Sparine®). Suitable for I.M. or I.V. use. The initial dose is 50-200 mg. depending upon the degree of excitation. Thereafter, give 50-200 mg orally or I.M. q 4 h.

2. Prochlorperazine (Compazine®), 5-10 mg orally or I.M. t.i.d.

3. Paraldehyde is useful in delirium (including delirium tremens). Barbiturates,

bromides, and opiates often increase the excitement of delirium but may be used in manic states. The ordinary stock paraldehyde solution needs no sterilization, and for that reason is available for immediate administration by any desired route. The oral route is preferred unless the patient is unable to swallow.

4 Chloral hydrate may be given instead of paraldehyde in doses of 2-8 ml ( $\frac{1}{2}$ -2 dr.) of the 25% stock solution or as capsules, 0.5-1 Gm ( $\frac{1}{4}$ -15 gr.) orally.

5 Scopolamine hydrobromide. For delirium without pain, 0.3-0.4 mg ( $\frac{1}{200}$ - $\frac{1}{150}$  gr.), 2-4 times daily may be valuable.

6 Morphine sulfate, 8-15 mg ( $\frac{1}{8}$ - $\frac{1}{4}$  gr.), with scopolamine hydrobromide, 0.3-0.4 mg ( $\frac{1}{200}$ - $\frac{1}{150}$  gr.), may be administered subcut when delirium is marked or is associated with or caused by pain.

7 Diphenylhydantoin (Dilantin®) 200-300 mg (3-5 gr.) per day, should be provided for those patients with symptoms or a history of convulsive seizures.

D Hydrotherapy. The wet pack is an effective technic which should be administered however, only by trained personnel. Constant supervision is required. Wet packs are contraindicated in patients who are physically weak or exhausted, are having convulsions, or who have significant cardiovascular disease. Vital signs must be observed at least every 15-20 minutes.

E Nutrition and Hydration. Unless there is a specific indication for hypohydration, a normal state of hydration should be maintained. This is especially true in the presence of fever. For delirium tremens of alcoholism, 1-2 L of 5-10% glucose solution containing 100 mg ( $\frac{1}{2}$  gr.) of thiamine hydrochloride and 100 mg ( $\frac{1}{2}$  gr.) nicotinic acid may be given daily. Attempt to maintain nutrition. Small frequent feedings are best tolerated.

F Psychiatric Care. If the measures outlined as mentioned above do not suffice, consider transfer to the psychiatric service.

#### Treatment of Delirium Tremens

Adequate sedation is mandatory in delirium tremens, and almost any sedative agent may be used, the phenothiazines, barbiturates, and paraldehyde are the most commonly used (Delirium tremens is probably the only alcoholic condition in which barbiturates and paraldehyde may be recommended). These must be given in large enough doses to sedate thor-

oughly. Sedation should be continued for several days after the delirium abates.

#### Prognosis

The prognosis depends in great part upon the reversibility of the causative factor. With adequate treatment most patients recover from the delirium, but occasionally death occurs after a few days to weeks. After recovery from delirium, the ultimate prognosis depends upon the underlying problem.

### CHRONIC BRAIN SYNDROME

#### Essentials of Diagnosis

- Slow deterioration of the higher mental processes (e.g., memory, retention, recall)
- Irritability, confusion, repetition
- Rigidity of behavior with narrow self-interest
- Frequently delusional somatic complaints
- Loss of power of abstract thinking

The various causes of chronic brain syndrome should be distinguished from each other since several of the causes are partially reversible or can be arrested with proper therapy.

#### General Considerations

Chronic brain syndrome is usually an irreversible impairment of cerebral function resulting from brain damage or atrophy. The most common cause is cerebral arteriosclerosis, beginning usually between the ages of 50 and 60. Other causes are intracranial neoplasms, intracranial infection, general paresis, presenile dementia of both Alzheimer's and Pick's diseases, Huntington's chorea, and some cases of Korsakoff's psychosis.

#### Clinical Findings

This disorder is manifested by general coarsening of the personality with loss of adaptability and decrease of mental function. The patient becomes crude and slovenly, both in speech and dress. The mood is labile, but irritability and anger are predominant. Memory and retention are defective; the patient is confused, unable to grasp subtleties, is rigid and stubborn, and tends toward pointless repetition of actions or words. His interests are narrow and self-centered. Somatic complaints are often present but are more often delusional than real. There may be evidence

of generalized arteriosclerosis. Specific neurologic defects may occur in cases caused by cerebrovascular accidents, tumors, paresis, and chorea.

Laboratory findings may be of value in the diagnosis of the specific etiologic disease, e.g., a positive CSF serology in paresis.

X-ray investigation may be useful, e.g., pineal gland shift in tumor, cerebral atrophy on pneumoencephalogram in presenile or senile dementia. EEG findings are frequently abnormal.

Psychologic testing (e.g., Rorschach Bender Visual Motor Gestalt Test, etc.) is frequently helpful in differentiating organic from psychogenic disorders.

### Treatment

Treatment consists of specific therapy of the underlying disease when possible. e.g., some patients with early paresis may respond favorably to penicillin. Otherwise treatment is primarily symptomatic and supportive. An effort should be made to manipulate the patient's environment in his favor. Pleasant, friendly surroundings and continued usefulness within the limits of the patient's ability are important therapeutic considerations. The patient should be confident that his physician will maintain a continuing interest in his welfare. The family should be encouraged to cooperate with the long-term treatment program; this may in fact be the single most important aspect of therapy.

Agitation may be controlled with promazine or related drugs, and night confusion minimized by leaving the room lighted.

### Prognosis

Most cases are progressive and irreversible, and custodial care in an institution is usually necessary. Depression and suicidal attempts are frequent.

## MENTAL DEFICIENCY (Mental Retardation)

Previous concepts of mental deficiency in terms of diagnostic entities based upon clinical impressions and empiric observations have fortunately been discarded. The terms "moron," "imbecile," and "idiot" no longer serve a useful purpose and can actually be misleading. Mental deficiency is now classified according to cause (e.g., hereditary, familial, or secondary to organic disease) and degrees of

deficiency are expressed as "borderline," "mild," "moderate," or "severe" according to the results of psychometric tests.

Psychometric tests should measure both the verbal IQ and the performance IQ as well as the so-called full-scale IQ. Discrepancies between the verbal IQ and the performance IQ are frequently reported. In borderline cases (IQ 75-85) it is essential to perform a battery of psychologic tests or to repeat certain tests in order to determine the validity of the results. Special attention must be paid to factors which may influence the validity of psychometric tests (e.g., educational limitations, language handicaps, defective vision or hearing, or marked anxiety or apprehension during the examination).

The social adjustment of a mentally defective person is usually more difficult than that of the normal person, and much depends upon early recognition of the problem, understanding and skillful social and vocational guidance. It is not uncommon for a maladjusted mentally retarded person to develop neurotic, sociopathic, or psychotic reaction mechanisms.

Many mentally retarded patients can learn to occupy a useful, productive, and acceptable place in society. Important aspects of the assistance program are a protective environment, understanding and accepting parents, friends, teachers, and physicians, and community facilities as indicated.

Woodward, K.E. Psychiatric study of mentally retarded preschool children: report of 4 year study. Arch Gen Psychiat 2: 156-70, 1960.



## PSYCHOPHARMACOLOGIC DRUGS

### SEDATIVE-HYPNOTIC DRUGS

Sedative or hypnotic drugs are CNS depressants which in small doses are used to relieve anxiety or to reduce spontaneous activity and, in larger doses, to induce sleep. Depending upon the dose, they may produce sedation, ataxia, excitement, sleep, general anesthesia with loss of protective reflexes, and respiratory depression. In addition, they are anticonvulsants and spinal cord depressants. Their use can lead to habituation and withdrawal convulsions.

#### Clinical Indications.

A. To decrease spontaneous activity, e.g., when bed rest is desirable, as in thyrotoxicosis.

B. For symptomatic relief of anxiety.

C. To encourage or induce sleep.

D. Special uses in anesthesia and pre-anesthesia.

#### Side Effects & Toxicity.

A. Hangover Depression that persists beyond a desired period may be unpleasant to the patient.

B. Ataxia and disinhibition comparable to the effects of alcohol.

C. Excitement comparable to stage II of general anesthesia. This effect is more common in young and aged patients and when a stimulus such as pain is also present.

D. Excessive depression with coma (general anesthesia) and respiratory and vasomotor depression.

E. Habituation.

F. Withdrawal Hyperexcitability or convulsions.

#### Cautions.

A. Use with special care in combination with other central depressants: alcohol, tranquilizers, morphine, and related drugs.

B. Hepatic insufficiency is usually said to be a relative contraindication to the use of these drugs because of the hazard of prolonged effect due to slow detoxification. Actually, the necessity for this precaution has not been borne out in clinical trial.

#### Classification & Choice of a Preparation.

Chemically this class of drugs is diverse and includes alcohols (ethyl alcohol, chloral hydrate, ethchlorvynol), urethanes (ethinamate, meprobamate), substituted ureas (of which the barbiturates may be considered a special class), and others. In their biologic properties they differ, practically speaking, only in their speed of onset and duration of action. All of the effects listed in the introductory paragraphs above are established for the drugs tabulated on p. 502.

The short-acting sedative hypnotics exert an effect soon after absorption (20-30 minutes), and their action persists for 3-4 hours. This group is useful for bedtime or preoperative medication.

The convenience and familiarity of pentobarbital (and its equivalent, secobarbital) have made it the most commonly used drug of the class. Alternative drugs, except perhaps chloral hydrate, offer no advantages.

The long-acting drugs are best used in repeated small doses for daytime sedation. They do not exert their maximum effects for several hours, and, if larger doses are used for hypnosis, the persistence of the effect leads to "hangover."

Chlordiazepoxide (Librium®) differs from phenobarbital only in the greater duration of its effect. The physician should recognize, however, that it is not distinct from other sedatives.

The hypnotics with intermediate properties have been most extensively used for the patient who falls asleep easily but, in his judgment, awakens prematurely. Recently they have been used also for the daytime relief of anxiety, usually under the impression that the newer drugs are somehow different from the more familiar amobarbital. Under controlled clinical trials neither the patient nor the physician can distinguish meprobamate from amobarbital. With full doses of both short-acting and intermediate-acting sedatives disinhibition is very common, and the euphoric effect has led to abuse.

## Sedative Hypnotic Drugs

Any of the drugs listed in this table may cause drowsiness, mental confusion, headache and euphoria or excitement. More severe toxicity is manifested by delirium, coma, slow and shallow respirations and circulatory collapse. Side effects peculiar to individual drugs in the list are noted below.

	Oral Dose		MLD†	Toxicity Reactions (in addition to those listed above)
	Hypnotic (Single Dose)	Sedative (3-4 Times a Day)		
<b>Short acting</b>				
Pentobarbital*‡	100-200 mg	30 mg	1.5 Gm.	
Secobarbital*‡	100-200 mg	30 mg	2 Gm	
Baraldehyde	12-16 ml		50 Gm	
Hexobarbital (Sombulex® Evipal®)	250-500 mg		2 Gm	
Ethinamate (Valmid®)	0.5-2 Gm		5 Gm	
Methypyrilone (Noludar®)	200-400 mg	50-100 mg	5 Gm	
Ethchlorvynol (Placidyl®)	0.5-1 Gm	100-200 mg	15 Gm	
Chloral hydrate	0.5-1 Gm		2 Gm	Gastric irritation
Chlorobutanol (Chloretone®)	0.5-1 Gm			
<b>Intermediate acting</b>				
Amobarbital*‡	100-200 mg	15-30 mg	1.5 Gm.	
Aprobarbital (Alurate®)	120 mg	20-40 mg	2 Gm	
Buobarbital (Butisol®)	100-200 mg	8-60 mg	2 Gm	
Winbarbital (Delvinol®)	100-200 mg	30 mg	2 Gm	
Heptobarbital (Medomin®)	200-400 mg	50-100 mg	2 Gm	
Meprobamate (Miltown® Equanil®)		400 mg	16 Gm	Purpura and other sensitivity reactions
Glutethimide (Doriden®)	500 mg		5 Gm	
<b>Long acting</b>				
Phenobarbital*		15-30 mg	1.5 Gm	
Meptobarbital (Mebaral®)		30-60 mg	2 Gm	
Ectylurea (Nostyn® Levanil®)		150-300 mg	15 Gm	
Chlordiazepoxide (Librium®)		5-10 mg (do not exceed 50 mg/day)	†	Long action leads to cumulative effects
Phenaglycodol (Ultran®)		200 mg	†	
Bromides	No longer prescribed but still used in proprietary mixtures			Acneiform rash, increased oral nasal and lacrimal secretions, Toxic psychosis

\*These barbiturates are also available as sodium salts for parenteral administration. Parenteral forms of other sedatives are available but experience with their use is limited.

†With the exception of 2 recently introduced drugs (phenaglycodol and chlordiazepoxide) each of the drugs listed has been used in successful suicidal attempts or has been lethal after therapeutic accidents.

‡Amobarbital, secobarbital and pentobarbital are unprotected compounds available from many manufacturers. They are also identified by the trade names of Amytal®, Seconal® and Nembutal®.

**Note:** The following sedatives are listed for purposes of identification only. They are rarely used or are present only in mixtures: Long acting: Barbital, carbromal, acetylcarbromal. Intermediate-acting: Butethal (Neonal®), cyclopal, diallylbarbituric acid, probarbital (Iprat®). Short acting: Cyclobarbital (Phanodan®), hexethal (Ortal®), talbutal (Lotusate®).

The action of methylparafynol (Dormilson®) is too feeble to permit classification.

## Phenothiazines &amp; Other Tranquillizers\*

Potent Agents	Dose (3-4 Times a Day)	Toxicity
Chlorpromazine (Thorazine®)†	25-50 mg.	Blood dyscrasias (especially promazine, triflupromazine, and trimeprazine), obstructive jaundice (especially chlorpromazine), parkinsonism, convulsions, drowsiness, dizziness, fever, postural hypotension, tachycardia, dry mouth, blurred vision, nasal congestion, and constipation. Promethazine is quite safe but produces much sedation.
Promazine (Sparine®)†	50-200 mg	
Promethazine (Phenergan®)†	25 mg.	
Triflupromazine (Vesprin®)†	10-20 mg	
Prochlorperazine (Compazine®)†	5-10 mg	
Trifluoperazine (Stelazine®)	1 mg	
Perphenazine (Trilafon®)†	2-4 mg	
Fluphenazine (Permitil®, Prolixin®)	1 mg (do not exceed 10 mg /day)	
Thioridazine (Mellaril®)	10-25 mg	
Thiopropazate (Dartal®)	10 mg	
Trimeprazine (Temaril®)	2.5 mg	
Chlorprothixene (Taractan®)†	25 mg	
Less Potent Agents		Less potent in that dose is limited by atropine-like side effects. No established usefulness.
Hydroxyzine (Atarax®, Vistaril®)†	25-50 mg.	
Mepazine (Pacatal®)†	25 mg	
Benactyzine (Suavitol®, Phobex®)	1-5 mg	
Bucilizine (Softran®)	50 mg	

\*The rauwolfia alkaloids (reserpine etc.) are rarely used in psychiatric practice. See ,

## Hypotensive Drugs

†Parenteral dose form for I. M. injection available. Use maximum of one oral dose.

Other phenothiazines equivalent to the above are advertised for specific purposes: pipamazine (Mornidine®) and thioethylperazine (Torecan®) as antiemetics, trimeprazine (Temaril®) and methdilazine (Tacaryl®) as antipruritic agents.

## Actions of Sedatives &amp; Phenothiazines

Sedatives (e.g., Phenobarbital, Meprobamate)	Phenothiazines (e.g., Promazine, Prochlorperazine)
With increasing doses <i>Relief of anxiety</i> Sedation and sleep Ataxia Excitement, drunkenness, disinhibition Anesthesia Respiratory and vasomotor depression and death	<i>Easy arousal</i> Extrapyramidal effects: parkinsonism, dystonias Convulsions Autonomic effects Antiemetic action Control of psychotic excitement <i>Potentiation of narcotic analgesics</i>
With continued administration Anticonvulsant action Habituation Voluntary muscle relaxation	

The "ultra-short-acting" compounds (e.g., thiopental) have a brief duration of action, and their use is limited to general anesthesia.

Any of the drugs listed in the table on p. 502 may cause drowsiness, mental confusion, headache, and euphoria or excitement. More severe toxicity is manifested by delirium, coma, slow and shallow respirations, and circulatory collapse.

### TRANQUILIZERS (Principally Phenothiazines)

In contrast to the sedative drugs, the tranquilizers can exert a calmative effect on agitated, hyperactive patients without impairing their ability to respond to ordinary stimuli. The tranquilizers have therefore found their greatest usefulness in the hospital care of psychotic patients. They are not useful and should not be used for the relief of neurotic anxiety of the type most commonly encountered in office practice. Some of the so-called tranquilizers (e.g., meprobamate) are actually useful in the control of simple anxiety and are actually sedatives and are listed in the table on p. 502.

The toxic effects of the tranquilizers include postural hypotension, sedation and atropine-like effects on the eyes, bladder, and pulse rate. Various extrapyramidal signs such as parkinsonism, paroxysmal dystonias, and uncontrollable restlessness may sometimes be relieved by antiparkinsonism drugs. Large doses may cause convulsions.

No superiority in therapeutic effect has been demonstrated for any one of the major tranquilizers. A few (see chart on p. 503) can be discarded because of their relative lack of potency. Promazine (Sparine®) administration has been associated with a significant number of cases of agranulocytosis. Thioridazine (Mellaril®) has caused many more cases of pigmentary infiltration of the retina than other phenothiazines in spite of its more recent introduction. The conservative practice would be to discontinue using chlorpromazine (Thorazine®), which in the past often caused obstructive jaundice (due to biliary stasis) on an allergic basis. The jaundice is reversible, and there is no serious hepatocellular damage. The incidence of jaundice associated with chlorpromazine administration has recently decreased remarkably.

The effects of tranquilizers are additive to those of other CNS depressants except for

the narcotic analgesics, the effects of which are greatly potentiated by tranquilizers.

The dosage of a tranquilizer for severe psychiatric disorders is increased at intervals of several days until a satisfactory response is obtained or until side effects limit the dose. In the table on p. 503 are listed the usual initial doses of these agents; they are given for the purpose of showing relative potency.

Parenteral preparations are available for the initiation of treatment of acute agitation due to organic (including alcoholic) or psychotic causes. The initial IM dose should be approximately the same as the oral dose.

### ANTIDEPRESSANT DRUGS

The antidepressant drugs may be used to terminate a depressive state or to minimize or even obviate the need for electroconvulsive therapy. Although the response is slower than the response to electroconvulsive therapy and although a successful result is not always achieved and it is impossible to predict which patients will respond, most psychiatrists now recommend a trial of drug treatment, beginning with imipramine (Tofranil®) (or equivalent), before electroconvulsive therapy is used. The hydrazides or "psychic energizers" may be used later if the patient fails to respond.

The amphetamine group of drugs is used in the U.S.A. for less severe depressive reactions.

Imipramine (Tofranil®) and amitriptyline (Elavil®) are chemically and pharmacologically similar to the tranquilizers. Side effects are similar to those of chlorpromazine but are less frequent. Begin dosage with 25 mg 3 times daily and increase as necessary to a maximum of 250 mg/day.

The hydrazides, also known as amine oxidase inhibitors and "psychic energizers," exert a persistent stimulant effect which becomes apparent after a latent period of days or weeks. Other drugs should not be given for at least 2 weeks after the hydrazides are discontinued. Undesirable side effects are in general due to excessive CNS stimulation and altered autonomic nervous system activity. They include hypotension, vascular headaches, flushing, constipation, edema, dry mouth, vertigo, decreased potency in the male, and nausea. Central stimulation may cause sleeplessness, hyperreflexia, agitation, and even a toxic psychosis. Anemia and peripheral neuropathy occur, but liver damage is rare with the drugs still available. A variety of

central depressants and hypotensive agents are potentiated by the hydrazides

Iproniazid (Marsilid<sup>®</sup>) and pheniprazine (Catron<sup>®</sup>) have been withdrawn from the market. The presently available drugs in this group are listed below.

The dosages of the useful sympathomimetic amines of the amphetamine type are given in the discussion of Obesity. Tranlycypromine (Parnate<sup>®</sup>) must still be regarded as an unestablished drug. Methylphenidate (Ritalin<sup>®</sup>) is comparatively ineffective and has not proved to be a useful drug.

#### Hydrazides

	Initial Dose (per day)	Maintenance Dose (per day)
Isocarboxazid (Marplan <sup>®</sup> )	20-30 mg	10 mg (maximum)
Nialamide (Niamid <sup>®</sup> )	100-300 mg	50-150 mg
Phenelzine (Nardal <sup>®</sup> )	30-45 mg	5-20 mg

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## Endocrine Disorders

Felix O. Kolb & Sheldon Margen

### The Difficulties of Diagnosis of Endocrine Diseases.

The diagnosis of endocrine disorders is complicated by the following factors peculiar to these organs:

**A Interrelationships of the Endocrine Glands** Because the endocrine glands are so closely interrelated, the presenting symptoms and signs of any endocrine disorder may represent a secondary disturbance in another gland or even in more than one gland. The diagnostic clue may therefore be in an organ which is secondarily affected by hypofunction or hyperfunction of the gland in question. For example, amenorrhea may be due to an abnormality of the pituitary or adrenal gland rather than to a primary ovarian lesion.

**B Homeostatic (Compensatory) Mechanisms** A well-balanced system of homeostasis often disguises the existence of pathologic changes in the pituitary which is inhibited by rising levels of secretions of the target glands.

**C Size of Lesion vs. Magnitude of Effect** The metabolic effect of an endocrine disturbance is not necessarily proportionate to the size of the lesion. A small tumor may cause extensive disturbance whereas a striking enlargement may have no pathologic significance except as a space-occupying lesion.

**D Physiologic vs. Pathologic States** The line between a physiologic aberration and a pathologic state may be quite tenuous (e.g., physiologic growth spurt vs. gigantism).

**E. Deficiencies of Knowledge** Some of the endocrine glands are activated by ill-defined neurohumoral factors presumably located in the hypothalamus. The diagnosis of disturbances along the pathway of this mechanism are largely beyond the reach of present-day medicine.

Direct chemical determinations of various hormones in blood and urine are being developed in increasing numbers, but until they are perfected less costly, and more generally available for clinical use, bedside observation and sensitive indirect diagnostic procedures are still required to establish the proper diagnosis of most endocrine disorders.

## NONSPECIFIC MANIFESTATIONS

### Delayed Growth

Growth delays due to endocrine and metabolic disorders are at times difficult to distinguish from familial or genetic dwarfism. Often there is an association with delayed genital development. Rule out bone diseases and nutritional, metabolic, and renal disorders which delay growth. Look for associated stigmas such as polydactyls and webbing. Plotting of the growth rate will demonstrate whether growth has been delayed since birth or only during a specific period in childhood. Hypothyroidism must be excluded, as it is at times subtle and can be diagnosed only by sensitive tests of thyroid function or by a trial of thyroid therapy. Epiphyseal dysgenesis (stippling) may be the telltale sign of juvenile hypothyroidism. The differentiation of hypopituitarism from delayed adolescence will become apparent in adult life. Dwarfing is also seen with gonadal dysgenesis in Turner's syndrome and with pseudohypoparathyroidism. A rapid growth spurt with eventual short stature is typical of sexual precocity and of the adrenogenital syndromes. In any problem of growth delay, obtain an accurate determination of bone age and an x-ray of the sella turcica, and measure the skeletal proportions carefully.

### Excessive Growth.

Excessive growth may be a familial or racial characteristic or a physiologic event (e.g., the growth spurt of puberty) as well as a sign of endocrine disease. If precocious

genital development occurs, consider true precocity due to pituitary or hypothalamic disorders, or pseudoprecocious puberty due to excess of adrenal, ovarian, or testicular hormones (often due to tumors). These patients, if not treated rapidly, will eventually be of short stature as a result of premature closure of their epiphyses. Pituitary eosinophilic tumors are rare before puberty; thereafter, they cause pituitary gigantism associated with enlargement of the sella turcica and visual field defects. After closure of the epiphyses acromegalic gigantism will result. Eunuchoid individuals tend to grow taller, with span exceeding height. Diabetic children are often tall.

### Obesity

Although obesity is a common presenting "endocrine" complaint, most cases are due to constitutional factors and excessive food intake. A sudden onset of massive obesity associated with lethargy or polyuria suggests a hypothalamic lesion (rare). While most cases of extreme obesity are associated with delayed puberty, slight excesses of food intake may lead to precocity. Hypothyroidism is usually not associated with marked obesity. In Cushing's disease or syndrome, there is moderate obesity with a characteristic "buffalo hump" and trunk obesity with thin extremities. Striae are common with any type of obesity. They are more often purplish in Cushing's syndrome. Amenorrhea, hypertension, and glycosuria are commonly associated with obesity, and improve after adequate weight loss. Islet cell adenomas are usually associated with obesity, but these are quite rare. In most instances the obese patient requires increased activity, reduction in caloric intake, and, at times, psychotherapy.

### Wasting & Weakness.

Pituitary cachexia (Simmonds' disease) is quite rare. Always rule out nonendocrine causes and consider anorexia nervosa and dietary fanaticism before looking for endocrine disturbances. Consider the possibility of diabetes mellitus, thyrotoxicosis, and Addison's disease if weight loss is progressive.

### Abnormal Skin Pigmentation or Color.

First consider normal individual, familial, and racial variations. Hyperpigmentation may coexist with depigmentation (vitiligo) in Addison's disease, which must be ruled out by standard tests. Search carefully for pigmentary spots on mucous membranes, gums, and nipples. Differentiate Addison's disease from

sprue, hemochromatosis, and argyria. Pregnancy and thyrotoxicosis are at times associated with spotty brown pigmentation, especially over the face (chloasma). Drug administration (e.g., diethylstilbestrol) will cause localized brown-black pigmentation over the nipples. Brown pigment spots with a ragged border are typical of Albright's syndrome (associated with fibrous dysplasia and precocious sexual development in the female), smooth pigmented nevi are seen in neurofibromatosis. Patients with Cushing's disease have a ruddy complexion, the hypogonadal or hypopituitary patient has a sallow, waxy, and at times yellowish or fawn color, and is unable to tan on exposure to sunlight.

### Hirsutism

Marked normal variations in the amount of body hair occur on a racial, familial, or genetic nonendocrine basis. Hirsutism, however, is one of the major presenting complaints of women and may be the first sign of a serious neoplastic disease, if so, it is rarely completely reversible even if the tumor is removed. Hirsutism is of greater significance if it occurs other than at puberty, with pregnancy, or at the menopause, if it is associated with other features of virilization, such as balding or enlargement of the clitoris, and if the onset is sudden. Always investigate the patient's adrenal status and rule out tumor and hyperplasia. Ovarian causes include polycystic ovaries (Stein-Leventhal syndrome), hilar cell tumors, arrhenoblastoma, and theca cell luteinization. As a minimum diagnostic procedure, a urinary 17-ketosteroid determination should be obtained. It is important to make certain that the patient has not received androgenic medication.

### Change in Appetite.

Polyphagia (associated with polydipsia and polyuria) is classically found in uncontrolled diabetes mellitus. However, excessive eating is usually not an endocrine problem but a compulsive personality trait. Only rarely is it due to a hypothalamic lesion, in which case it is associated with somnolence and other signs of the hypothalamic disease (Fröhlich's syndrome). Excessive appetite with weight loss is observed in thyrotoxicosis, polyphagia with weight gain may indicate acromegaly or hypoglycemia due to an islet cell adenoma.

Anorexia and nausea associated with weight loss and diarrhea may occur at the onset of addisonian crisis or uncontrolled diabetic acidosis. Anorexia and nausea with constipation are found with any state of hypercalcemia, e.g., hyperparathyroidism, and may

be indistinguishable from the same symptoms occurring in peptic ulcer (which may coexist\* with hyperparathyroidism)

### Gynecomastia

Enlargement of one or both breasts usually painless and of rapid onset is a common finding in adolescent boys. It may also be seen in old men. It is usually transient and of little significance. One must differentiate between true glandular enlargement and simple fat pads or ballooning of the areolar tissue. Any painless hard lump, especially if unilateral, may be carcinoma.

True gynecomastia is found in many endocrine and nonendocrine disorders, e.g., thyrotoxicosis, liver disease, paraplegia, and adrenal tumors. If associated with small testicles and lack of sperm, it may be part of Klinefelter's syndrome. Obtain a buccal smear, which may indicate a female nuclear chromatin pattern.

Breast enlargement and tenderness may be due to estrogen therapy, but also occur after the administration of androgens, especially to eunuchoid patients.

Gynecomastia may be the presenting sign of serious testicular tumors, such as chorio carcinoma, which may be too small to be palpable yet may metastasize widely.

Breast enlargements may be transitory or may persist even after the cause (e.g., exogenous estrogen) is removed. Surgical removal is often necessary for cosmetic reasons.

### Abnormal Lactation

Lactation is a physiologic phenomenon when seen in the newborn (with its milk) may occur before menstruation and is part of the syndrome of pseudocyesis. It is frequently present in both sexes in acromegaly and more rarely in thyrotoxicosis. In some patients with *chromophobe adenomas of the pituitary* (Chiari Frommel syndrome with amenorrhea) lactation may be so profuse that it is distressing to the patient. Abnormal lactation occurs rarely with estrogen-secreting adrenal tumors and quite rarely with corpus lutein cysts and chorio epithelioma. Some drugs (e.g., chlorpromazine) may produce lactation.

### Polyuria & Polydipsia

Polyuria, commonly associated with polydipsia, is usually of nonendocrine etiology due to a habit of drinking excessive water (psychogenic). However, if it is severe and of sudden onset, it suggests diabetes mellitus or diabetes insipidus. Diabetes insipidus may develop insidiously or may appear suddenly

after head trauma or brain surgery. Always attempt to rule out an organic lesion in or about the posterior pituitary-supraoptic tract. In children one must consider nephrogenic diabetes insipidus and eosinophilic granuloma.

A urine specific gravity over 1.016 virtually rules out diabetes insipidus.

Polyuria and polydipsia are frequently seen in any state of hypercalcemia, such as hyperparathyroidism, and are also part of the syndrome of aldosteronism, in which they are typically nocturnal. Polyuria may occur in renal tubular disorders, such as renal tubular acidosis and Fanconi's syndrome.

### Renal Colic, Gravel & Stone Formation

A metabolic cause must be sought for recurrent stone formation and for kidney stones in children. If there is a family history, cystinuria and uric acid stones must be considered, or renal tubular acidosis with nephrocalcinosis. About 5% of stones are due to hyperparathyroidism, which must be ruled out in every instance of calcium stones. Look for bone disease, especially subperiosteal resorption of the bones of the fingers. Look also for signs of osteomalacia associated with excessive renal loss of calcium. Vitamin D intoxication, sarcoidosis, and excessive intake of milk and alkali must be considered. Any rapid bone breakdown may give rise to renal calcium stones, e.g., in Paget's disease. Uric acid stones may occur in patients with gouty arthritis who are receiving uricosuric agents and also after any type of intensive therapy for leukemia or polycythemia. Oxaluria is a rare cause of severe renal calcification and may be associated with deposition of oxalate in soft tissues (oxalosis). At times stones form in a structurally abnormal kidney (e.g., medullary sponge kidney). Metabolic causes of renal stones must be corrected early before renal damage occurs, since renal injury may not be reversed upon removal of the initiating factor. The key to proper diagnosis is a careful stone analysis.

### Precocious Puberty (in Both Sexes)

Precocious puberty is often a familial trait, but it may indicate serious organic disease. One must differentiate true precocity from pseudoprecocity. Hypothalamic lesions, encephalitis, and certain tumors (e.g., hamartoma of the tuber cinereum) may cause true sexual precocity. The same is found in girls who have associated fibrous dysplasia of bone and pigment spots (Albright's syndrome). Adrenal hyperplasia or tumor and gonadal tumors usually cause pseudoprecocious puberty with feminization or virilization. The cause must be detected early since almost all children with precocious puberty will eventual



ly be short or even dwarfed as a result of premature closure of the epiphyses - and because many of these tumors are potentially malignant.

#### Sexual Infantilism & Delayed Puberty.

It is often difficult to differentiate between simple functional delay of puberty and organic causes for such delays. Any type of gonadal defect may be manifested primarily by failure of normal sexual development. Many patients grow to eunuchoid proportions, with span exceeding height. Consider hypothalamic lesions, craniohypopharyngioma, pituitary tumors, and defective testes or ovaries, and look for associated stigmas (webbed neck of Turner's syndrome, gynecomastia of Klinefelter's syndrome). Pituitary gonadotropin and urinary steroid excretion studies may help classify these disorders. Determine chromatin sex pattern on a buccal smear.

#### Lack of Potency & Libido in Males.

Almost all cases are psychogenic in origin and are not helped by hormone therapy. Occasionally, however, lessening of sex desire or impairment of function may be the presenting sign of pituitary adenoma, Addison's disease, or testicular damage. The earlier in life the deficiency makes its appearance, the more pronounced is loss of libido associated with genital hypoplasia. Diabetes mellitus and thyrotoxicosis may first become manifest with this complaint. Be sure to rule out estrogenic or feminizing tumors of the testis or adrenal and search for other signs of feminization, such as gynecomastia. Most patients will require psychotherapy.

#### Cryptorchism.

Failure of descent of the testes is often of great concern to parents, but it is not usually a medical problem since the testes, if present, will descend spontaneously at or shortly after puberty. They may descend after application of heat to the scrotum, as in a warm bath, which demonstrates that they are present and will later descend normally through an unimpeded passageway.

There is no agreement about when hormonal therapy should be instituted. If the testes are present, gonadotropic hormone will bring them down unless a hernia or blockage of the passageway prevents their descent. If there is doubt about whether the testes are present or not, obtain a buccal smear to determine the sex chromatin pattern.

Early surgical repair is advisable because intra-abdominal testes may later fail to produce sperm normally and because the incidence of malignancy in intra-abdominal testes is high.

Cryptorchism may be associated with hypogonadism or may be part of pseudohermaphroditism.

#### Bone & Joint Pains & Pathologic Fractures.

If the onset is at an early age and if there is a family history of similar disorders, consider osteogenesis imperfecta (look for blue sclerae). Bowing of the bone and pseudofractures suggest rickets or osteomalacia, due either to intestinal or, more commonly, renal tubular disorders. If bone pain, bone cysts, and fractures are associated with renal stones, consider hyperparathyroidism. Back pain with involvement of the spine suggests osteoporosis, especially when it occurs after the menopause. Aches and pains in the extremities are suggestive of rickets or osteomalacia. Rule out metastatic tumors, multiple myeloma and Paget's disease in elderly patients. Differentiate metabolic from nonmetabolic bone disorders. In doubtful cases, bone biopsy is indicated.

#### Tetany & Muscle Cramps.

Mild tetany with paresthesias and muscle cramps is usually due to hyperventilation resulting from an anxiety state. If tetany occurs in children rule out idiopathic hypoparathyroidism or pseudohypoparathyroidism. Look for calcification in the lens, poor teeth, and x-ray evidence of basal ganglia calcification. Consider hypoparathyroidism in the post-thyroidectomy patient. Tetany may be the presenting complaint of osteomalacia or rickets. Neonatal tetany is common and is probably due to the high phosphate content of milk and relative hypoparathyroidism. A similar mechanism has been considered responsible for leg cramps during pregnancy. Severe hypocalcemic tetany will occasionally produce convulsions and must be differentiated from "idiopathic" epilepsy. Also consider hypoglycemia, since it may be correctible. Classic signs of tetany are Chvostek's sign and Trousseau's phenomenon. If associated with hypertension and polyuria, consider primary aldosteronism. Leg cramps may occur in some diabetic patients.

#### Mental Changes.

Disturbances of mentation are often subtle and may be difficult to recognize, but they may be important indications of underlying endocrine disorders. Nervousness and excitability are characteristic of hyperthyroidism, pheochromocytoma, and hypoparathyroidism. Convulsions with abnormal EEG findings may occur in hypocalcemic tetany or in hypoglycemia, either spontaneous or induced by insulin. Pituitary tumors may cause sudden loss of consciousness, somnolence and prolonged

lethargy, or coma. Coma may occur in diabetic acidosis. Mental confusion may occur in hypopituitarism or Addison's disease or in long-standing myxedema. Mental deterioration is the rule in long-standing and untreated hypoparathyroidism and hypothyroidism (cretinism). Insomnia and psychosis is part of Cushing's syndrome, either spontaneous or induced. Early detection may prevent permanent brain damage. Mental deficiency may be associated with abnormal excretion of amino acids in the urine (e.g., phenylketonuria) and with chromosomal abnormalities.

## DISEASES OF THE PITUITARY GLAND

### PANHYPOPITUITARISM & HYPOPITUITARY CACHEXIA (Simmonds' Disease)

#### Essentials of Diagnosis

- Sexual dysfunction, weakness, lack of resistance to stress, cold, and fasting, axillary and pubic hair loss
- Low BP, may have visual field defects.
- All low: BMR, FFI,  $^{131}\text{I}$  uptake, FSH, urinary 17-ketosteroids and corticoids
- X-ray may reveal sellar lesion

Simmonds' disease is difficult to differentiate from anorexia nervosa, but in the latter cachexia is more common and loss of axillary and pubic hair less common. Urinary FSH and ketosteroid determinations may aid differentiation, however, a final diagnosis may depend upon the response to psychotherapy and medical management. Distinguish also from primary adrenal and primary thyroid disease.

#### General Considerations.

Hypopituitarism is a relatively rare disorder in which inactivity of the pituitary gland leads to insufficiency of the target organs. All or several of the tropic hormones may be involved. Isolated defects, e.g., of the gonadotropins, are not rare. There is also great variation in the severity of the lesions, from those merely involving pathways (hypothalamic lesions) to almost complete destruction of the gland itself. The etiology of this disorder includes circulatory collapse due to hemorrhage following delivery and subsequent pituitary

necrosis (Sheehan's syndrome), granulomas cysts and tumors (Rathke's pouch cyst, chromophobe adenoma), surgical hypophysectomy and functional hypopituitarism as seen in starvation and severe anemia. True pituitary cachexia (Simmonds' disease) is quite rare.

#### Clinical Findings.

These vary with the degree of pituitary destruction, and are related to the lack of hormones from the "target" endocrine gland.

**A Symptoms and Signs** Weakness, lack of resistance to cold, to infections, and to fasting, and sexual dysfunction (lack of development of primary and secondary sex characteristics, or regression of function) are the most common symptoms. In expanding lesions of the sella, interference with the visual tracts may produce loss of temporal vision, whereas a craniopharyngioma may cause blindness. Short stature is the rule if the onset is during the growth period.

In both sexes there is sparseness or loss of axillary and pubic hair, and there may be thinning of the eyebrows and of the head hair, which is often silky.

The skin is almost always dry, with lack of sweating, has a peculiar pallor, and is sallow ('fawn'-colored). Pigmentation is lacking even after exposure to sunlight. Fine wrinkles are seen, and the facies present a "sleepy appearance."

The heart is small and the BP low. Orthostatic hypotension is often present. Abnormal lactation may occur.

**B Laboratory Findings** The fasting blood sugar is usually low with a flat glucose tolerance curve. The insulin tolerance test (use only 0.05 units/Kg. I.V.) shows insulin sensitivity and is dangerous in these patients since severe reactions may occur. The BMR is usually low. The FFI level is low normal. Radioactive iodine uptake is low, with a rise following TSH (this does not occur in primary myxedema). Urinary 17-ketosteroids and corticoids are low, but rise slowly after corticotropin administration (this does not occur in primary Addison's disease). Both TSH and corticotropin may have to be given for several days. The metapyrone (SU-4885) test has recently been used to demonstrate limited pituitary reserve. Urinary gonadotropins (FSH) are very low, usually less than 3 mouse units/24 hours. Anemia is common.

**C. X-ray Findings** X-rays of skull may show a lesion in or above the sella. In growing children one may find delay in bone age.

**D Eye Examination** Visual field defects may be present.

### Differential Diagnosis.

The most difficult problem is differentiation from anorexia nervosa, which may simulate hypopituitarism. In fact, severe malnutrition may give rise to functional hypopituitarism. By and large, cachexia is far more common in anorexia nervosa, and loss of axillary and pubic hair is rare, at times mild facial and body hirsutism is seen in anorexia nervosa. The 17-ketosteroids are low normal or not as low as in hypopituitarism, and may respond to corticotropin stimulation, and the urinary gonadotropins are usually present at levels of 3 mouse units/24 hours. The response to diet and psychotherapy at times settles the diagnosis.

Primary Addison's disease and primary myxedema are at times difficult to differentiate from pituitary insufficiency, but the response to corticotropin and TSH often helps.

At times hypopituitarism may masquerade as "nephrosis" or as "pernicious anemia".

The severe hypoglycemia after fasting may cause confusion with hyperinsulinism.

The mental changes of hypopituitarism may be mistaken for a primary psychosis.

### Complications

In addition to those of the primary lesion (e.g., tumor), complications may develop at any time as a result of the patient's inability to cope with minor stressful situations. This may lead to high fever, shock, coma, and death. Sensitivity to thyroid may precipitate an adrenal crisis when thyroid is administered. Cortisones may cause psychosis.

### Treatment.

There is no readily available effective pituitary replacement preparation, therapy must therefore be aimed at correcting the end-organ deficiencies. This must be continued throughout life. Almost complete replacement therapy can be carried out with cortisone, thyroid, and sex steroids.

**A. Cortisones** Since edema is common with cortisone treatment, prednisone or dexamethasone (Decadron<sup>®</sup>) is preferable. Give prednisolone, 2.5-10 mg orally daily in divided doses, or dexamethasone, 0.5-2 mg orally in divided doses.

**B. Thyroid** Thyroid (and insulin) should rarely, if ever, be used in panhypopituitarism unless the patient is receiving cortisone. Because of lack of adrenal cortical function, pa-

tients are exceedingly sensitive to these drugs. For this reason one should exercise special care in differentiating myxedema from hypopituitarism - often a difficult problem.

Begin with small doses of 15-30 mg ( $\frac{1}{4}$ - $\frac{1}{2}$  gr.) daily and gradually increase to tolerance 60-100 mg ( $1\frac{1}{2}$  gr.) is usually adequate.

### C Sex Hormones

**1 Testosterone** or one of the newer anabolic steroids, e.g., fluoxymesterone (Halotestin<sup>®</sup>) (see p. 580) may be used in both males and females, primarily for their tissue building (protein anabolic) effect. For males give one of the longer-acting parenteral testosterone preparations every 3-4 weeks, or methyltestosterone, 10-20 mg orally daily. In females the dosage of these drugs is half that for males. If signs of virilizing action appear in the female, the drug should be withdrawn and they will lessen. They do not usually occur if the dose of methyltestosterone is kept under 300 mg/month. Fluoxymesterone may be given in doses of 2-10 mg orally daily.

**2 Estrogens** are useful in the female for their mild anabolic effect, their effect on secondary sex characteristics, and their possible neutralizing effect on androgens. Give diethylstilbestrol, 0.5-1 mg daily orally, ethinyl estradiol, 0.02-0.05 mg daily orally, or estrone sulfate (Premarin<sup>®</sup>), 0.625-1.25 mg daily orally.

**3 Chorionic gonadotropic hormones (APL<sup>®</sup>)** may be used in an attempt to produce fertility.

**Note:** Sex hormones, especially estrogens, should be employed cautiously in young patients with panhypopituitarism or the epiphyses will close before maximum growth is achieved. Most androgens, with the possible exception of fluoxymesterone, also share this property - especially when given in large doses.

**D. Human Growth Hormone** This hormone is by far the most effective agent for increasing height without closing the epiphyses, but it is available for only a few patients.

### Prognosis

This depends on the primary cause. If it is due to postpartum necrosis (Sheehan's syndrome), partial or even complete recovery may occur. Functional hypopituitarism due to starvation and similar causes may also be corrected.

If the gland has become permanently destroyed the problem is to replace target hormones, since replacement with pituitary tropic hormones is not yet feasible. It is pos-

sible to prolong life if states of stress such as starvation infection or trauma are treated with prompt and adequate replacement therapy. If the onset of the disease is in childhood the patient's ultimate height will be subnormal unless human growth hormone is used. Surgical procedures e.g. hypophysectomy to preserve vision in chromophobe adenomas have become safer since the advent of cortisone.

Bauer H G Endocrine and other clinical manifestations of hypothalamic disease  
J Clin Endocrinol 14 13 31 1954

Peters J P & others Functions of gonads thyroid and adrenals in hypopituitarism  
Metabolism 3 118 37 1954

Williams E Anorexia nervosa a somatic disorder  
Brit M J 2 190 5 1958

### HYPERPITUITARISM (Eosinophilic Adenoma of the Anterior Pituitary) GIGANTISM & ACROMEGALY

#### Essentials of Diagnosis

- Excessive growth of hands (increased glove size) feet (increased shoe size) jaw (protrusion of lower jaw) and internal organs or gigantism before closure of epiphyses
- Amenorrhoea headaches visual field loss sweating weakness
- Elevated serum inorganic phosphorus and BMR FBT normal glycosuria
- X ray Sellar enlargement and terminal phalangeal tufting

Hyperpituitarism is to be considered in unexplained amenorrhoea insulin resistant diabetes mellitus or goiter elevated BMR which does not respond to antithyroid drugs and too rapid growth or resumption of growth once stopped.

#### General Considerations

An excessive amount of growth hormone presumably due to overactivity of the eosinophilic portion of the anterior lobe of the pituitary is most often produced by a benign adenoma. The tumor may be small or rarely located within the sinuses rather than within the sella. The disease may be associated with adenomas elsewhere such as in the parathyroids or pancreas. If the onset is before closure of the epiphyses gigantism will result. If the epiphyses have already closed

at onset only overgrowth of soft tissues and terminal skeletal structures (acromegaly) results.

#### Clinical Findings

**A Symptoms and Signs** Crowding of other hormone producing cells especially those concerned with gonadotropic hormones causes amenorrhoea and loss of libido. Production of excessive growth hormone causes enlargement of the hands (spade-like) feet jaw face tongue and internal organs wide spacing of the teeth and an oily tough furrowed skin with multiple fleshy tumors (mollusca). Pressure of the pituitary tumor causes headache bitemporal hemianopsia lethargy and diplopia. In long standing cases secondary hormonal changes take place including diabetes mellitus goiter and abnormal lactation. Less commonly these may be the presenting picture in acromegaly. Excessive sweating may be the most reliable sign at onset of the disease.

**B Laboratory Findings** Serum inorganic phosphorus may be elevated (over 4 mg/100 ml) during the active phase of acromegaly. The urinary FSH level is usually low but it may be normal or even high. Glycosuria and hyperglycemia may be present and there is resistance to the administration of insulin. The BMR may be elevated. The FBT may be normal and may not fall after antithyroid medication. 17 Ketosteroids may be high or low depending upon the stage of the disease. Immunologic assays for growth hormone in blood (not generally available) show high levels.

**C X ray Findings** X ray of the skull may show a large sella with destroyed clinoids but a sella of usual size does not rule out the diagnosis. The frontal sinuses may be large. It may also demonstrate thickening of the skull and long bones with typical overgrowth of vertebral bodies and severe spur formation. Typical tufting of the terminal phalanges of the fingers and toes may be demonstrated. Dorsal kyphosis is common.

**D Eye Examination** Visual field examination may show bitemporal hemianopsia.

#### Complications

Complications include pressure of the tumor on surrounding structures rupture of the tumor into the brain or sinuses the complications of diabetes cardiac enlargement and cardiac failure. The carpal tunnel syndrome due to compression of the median nerve at the wrist may cause disability of the hand.

## Treatment.

The current majority opinion is that the treatment of choice of active tumors without visual field loss is pituitary irradiation, with or without the use of sex hormones. If visual fields are markedly reduced, x-ray therapy may be hazardous and surgery is the treatment of choice. In the "burnt out" case hormonal replacement as for hypopituitarism is required.

## Prognosis.

Prognosis depends upon the age at onset and, more particularly, the age at which therapy is begun. Secondary tissue and skeletal changes do not respond to removal of the tumor. The patient may succumb to the complications. The tumor may "burn out," causing symptoms of hypopituitarism.

Hamwi, G. J., & others: *Acromegaly* Am J Med. 29 690-9, 1960

## DIABETES INSIPIDUS

### Essentials of Diagnosis

- Polydipsia (4-40 L./day), excessive polyuria
- Urine sp. gr. < 1.006
- Inability to concentrate urine on fluid restriction.
- Vasopressin reduces urine output

The differentiation from nephrogenic and from psychogenic diabetes insipidus (pathologic water drinkers) often requires special tests. If tests indicate true diabetes insipidus, a search for the primary disease (e.g., tumor) should be made. Polyuria and polydipsia are also seen in diabetes mellitus, chronic nephritis, hypercalcemic states, and aldosterone-producing tumors.

### General Considerations.

Diabetes insipidus is an uncommon disease of young adults (particularly males) which is characterized by an increase in thirst and the passage of large quantities of urine of a low specific gravity. The urine is otherwise normal. The disease may occur acutely, e.g., after head trauma or surgical procedures near the pituitary region, or may be chronic and insidious in onset. It is due to insufficiency of the posterior pituitary or impaired function of the supraoptic pathways which regulate water metabolism. More rarely, it is due to unresponsiveness of the kidney to pitressin (nephrogenic diabetes insipidus).

The causes may be classified as follows:

### A. Due to Deficiency of Pitressin:

1. Primary diabetes insipidus, due to a defect inherent in the gland itself (where no organic lesion is demonstrable), may be familial, occurring as a dominant trait, or, more commonly, sporadic or "idiopathic."

2. Secondary diabetes insipidus is due to destruction of the functional unit by trauma, infection (e.g., encephalitis, tuberculosis, syphilis), primary tumor or metastatic tumors from the breast or lung (common), vascular accidents (rare), and xanthomatosis (eosinophilic granuloma of Hand-Schüller-Christian disease).

B. "Nephrogenic" diabetes insipidus is due to a defect in the kidney tubules which interferes with water reabsorption and occurs as a sex-linked, recessive trait. Patients with this type of the disease are the so-called "water babies." At times this type is acquired, e.g., after pyelonephritis. The disease is unresponsive to vasopressin.

### Clinical Findings

A. Symptoms and Signs. The outstanding signs and symptoms of the disease are intense thirst and polyuria, the volume of ingested fluid varying from 4-40 L. daily, with correspondingly large urine volumes. Restriction of fluids causes marked weight loss, dehydration, headache, irritability, fatigue, muscular pains, hypothermia, and tachycardia.

B. Laboratory Findings. A polyuria of over 6 L./day with a specific gravity below 1.006 is highly suggestive of diabetes insipidus, and a specific gravity of 1.015 or higher after fluid restriction rules out the disease. Special tests have been devised to distinguish true diabetes insipidus from psychogenic diabetes insipidus (Hickey-Hare and Carter-Robbins tests). The latter will respond (with reduction in urine flow and increase in urinary specific gravity) to administration of hypertonic (3%) saline solution, true diabetes insipidus does not. A response to vasopressin (Pitressin<sup>®</sup>) rules out "nephrogenic" diabetes insipidus. The serum calcium and potassium levels are normal.

If true primary diabetes insipidus seems likely on the basis of these tests, search for a possible brain lesion with x-rays of the skull, visual field tests, and encephalograms. Search also for associated bone lesions of xanthomatosis and obtain biopsy for confirmation. Look for a primary tumor in the lung or breast. In nephrogenic diabetes insipidus rule out pyelonephritis or hydronephrosis.

**Differential Diagnosis**

The most important differentiation is from the psychogenic water habit (see above). Polydipsia and polyuria may also be seen in diabetes mellitus, chronic nephritis, aldosteronism and in hypercalcemic states such as hyperparathyroidism. The low fixed specific gravity of the urine in chronic nephritis does not rise after administration of vasopressin. On the other hand in spite of the inability of patients with diabetes insipidus to concentrate urine, other tests of renal function yield essentially normal results (the NPV may even be below normal).

**Complications**

If water is not readily available the excessive output of urine will lead to severe dehydration which rarely proceeds to a state of vasomotor collapse and shock. Insomnia and dysphagia may occur. All the complications of the primary disease may eventually become evident.

**Treatment**

**A. Specific Measures.** Vasopressin tannate (Pitressin Tannate<sup>®</sup>) 1/2-1 ml in oil I.M. is the treatment of choice. It is effective for 24-72 hours. It is usually best to administer the drug in the evening so that maximal results can be obtained during sleep. Patients learn to administer the drug themselves and the dosage is adjusted as necessary. Warn the patient to shake well before filling the syringe. Posterior pituitary snuff inhaled 2-3 times a day may be used and is the most economical form of treatment but it may be quite irritating and absorption is uncertain. The dose varies from 30-60 mg. Aqueous vasopressin injection is rarely used in continuous treatment because of its short duration of action (1-4 hours). An occasional patient is allergic to animal vasopressin; a synthetic substitute will soon be available in a nasal spray.

**B. General Measures.** Mild cases (or vasopressin-resistant cases) require no treatment other than adequate fluid intake. Hydrochlorothiazide (Hydro Diuril<sup>®</sup>) 50-100 mg/day (with KCl) is of some help in reducing the urine volume of true or nephrogenic diabetes insipidus.

**C. X-ray therapy** may be used in the treatment of some cases due to tumor (e.g. eosinophilic granuloma).

**Prognosis**

Diabetes insipidus may be fatal especially if there is associated lack of anterior

pituitary function and may be transient e.g. following head trauma. The ultimate prognosis is essentially that of the underlying disorder. Since many cases are associated with organic brain disease the prognosis is often poor. Surgical correction of the primary brain lesion rarely alters the diabetes insipidus.

If the disease is due to an eosinophilic granuloma of the skull temporary amelioration or even complete cure may be effected with x-ray therapy.

The prognosis of the nephrogenic type is only fair since intercurrent infections are common especially in infants affected with the disease. The acquired forms of this type may be reversible if urinary tract infection or obstruction is alleviated.

Thomas W. C. Diabetes insipidus J Clin Endocrinol 17:565-82, 1957

## DISEASES OF THE THYROID GLAND

Thyroid hormone affects cellular oxidative processes throughout the body. It is normally elaborated within the follicles of the gland by a combination of inorganic iodine which is trapped by the gland under the influence of pituitary TSH and tyrosine forming moniodotyrosine and diiodotyrosine which further combine to form thyroxine and triiodo thyronine ( $T_3$ ), the principal hormones of the gland. The storage form of the hormone is thyroglobulin, a combination of thyroxine and thyroid globulin and it is in this colloidal form that the hormone is found within the follicles.

Under the influence of TSH the active hormones are released from the gland as the need arises. They can be measured as

protein bound iodine, the normal levels ranging from 4-8 mcg/100 ml. The requirements for iodine are minimal (about 200 mcg/day) but if a true deficiency arises or if the demand for iodine is increased (e.g. during puberty) hormone production will be insufficient and circulating levels will be low. This leads to increase in pituitary TSH output and hyperplasia of the thyroid gland follows.

Thyroid disorders may occur with or without diffuse or nodular enlargement of the gland (goiter). Symptoms may be due to pressure alone or to hyperfunction or hypofunction.

Since thyroid hormone affects all vital

processes of the body, the time of onset of a deficiency state is most important in mental and physical development. Prolonged insufficiency which is present since infancy (cretinism) causes irreversible changes. Milder degrees of hypofunction, especially in adults, may go unrecognized or may masquerade as symptoms of disease of another system, e.g., menorrhagia. Diagnosis will then depend to a large extent upon laboratory aids.

In any age group, whenever an isolated thyroid nodule is felt which is not associated with hyperfunction or hypofunction - and especially if there is any change in size of the nodule - the possibility of neoplasm must be considered.

Hamolsky, M. W., & A. S. Freedberg. The thyroid gland, *New England J. Med.* 262: 23-8, 70-8, and 129-37, 1960.

Werner, S. C., *The Thyroid: A Fundamental and Clinical Text*, Hoeber, 1955.

## TESTS OF THYROID FUNCTION

**Basal Metabolic Rate (BMR)** (With or without sedation)

Normal  $\pm 20\%$ .

### A. Elevated.

1. Markedly elevated - Hyperthyroidism, polycythemia, leukemia, pheochromocytoma.

2. Moderately elevated - Hyperthyroidism, anemia, congestive heart failure, Paget's disease, gigantism and acromegaly, malignancy, pregnancy, drugs (e.g., caffeine).

3. Slightly elevated - Febrile illnesses (1% per degree F. above normal), anxiety.

B. Low: Myxedema (-30% to -60%). Low rates are also found in panhypopituitarism, Addison's disease, anorexia nervosa, chronic debility, starvation, and also at times in nephrosis.

Usual Test Results in Thyroid Disorders\*

Condition	BMR	PBI-131 or $I^{131}$ Uptake	PBI	Other Useful Tests
Diffuse toxic goiter	H	H	H	Suppression test negative.
Toxic nodular goiter	H	H or N	H	Suppression test negative.
Pregnancy	H	H	H	Suppression test normal.
$T_4$ toxic factitia	H	L	H	
$T_3$ toxic factitia	H	L	L	
TSH injection	H	H	H	
Primary hypothyroidism	L	L	L	TSH test negative.
Pituitary hypothyroidism	L	L	L	TSH test negative.
Subacute thyroiditis	H or N	L	H	TSH test negative, antibody test positive.
Hashimoto's thyroiditis	H or L	N or H	N or L	Perchlorate and antibody tests positive.
Riedel's struma (early)	N	N	N	
Riedel's struma (late)	L	L	L	TSH test negative.
Thyroid cancer	N	N	N	TSH and suppression tests normal.
Nontoxic goiter	N	N or H	N or L	Suppression test usually normal.
Goitrous cretinism	L	H	L	Perchlorate test may be positive.
"Hot" nodule in euthyroidism	N	H	N	Scintigram, suppression test negative.
Methimazole treatment	N or L	L	N or L	
Post-methimazole rebound	N	H	N	
Cirrhosis	N	N or H	L, N, H	
Uremia	N	L, N, H	N	
Mercurial (diuretic)	N	N	L	
Iodide compounds	N	L	H	

\*Reproduced, with permission, from Williams, *Textbook of Endocrinology*, 3rd Ed. Saunders, 1962.

N = Normal; H = High; L = Low.

**Protein-Bound Iodine (PBI, "Hormonal Iodine")**  
Normal 4-8 mcg /100 ml serum.

**A Elevated** In hyperthyroidism, thyroiditis, and due to administration of iodides desiccated thyroid, or thyroxin inorganic iodides increase levels for up to 3 weeks, organic iodides (e.g., in urograms, cholecystograms) for 6 months or longer, oil-soluble organic iodides (e.g., Lipiodol<sup>®</sup>) for months to years

**B Low Hypothyroidism** Falsely low levels may be due to mercurial diuretics (low for 3-7 days), urinary loss of protein (e.g., in nephrosis), or T<sub>3</sub> (Cytomel<sup>®</sup>) administration

The BEI (butanol extractable iodine) test roughly parallels the PBI and is not affected by inorganic iodides. It is, however, raised by organic iodides. Normal 3-7 mcg /100 ml

**Radiolodine (<sup>131</sup>I) Uptake of Thyroid Gland**  
Normal 10-40% in 24 hours

**A Elevated** Thyrotoxicosis, hypofunctioning large goiter iodine lack

**B Low** Administration of iodides (similar to factors raising the PBI), T<sub>4</sub> antithyroid drugs, thyroiditis, myxedema, hypothyroidism

A scintigram over the gland outlines areas of increased and decreased activity. Suppression of uptake after administration of 75 mcg of T<sub>4</sub> daily for several days will determine if the area in the gland is autonomous or TSH-dependent. Administration of TSH for 2 or more days with increase in <sup>131</sup>I uptake over low control levels indicates the presence of thyroid tissue, and hence shows that low uptake was due to lack of TSH.

**Radioactive T<sub>3</sub> Uptake of Red Cells**  
Normal Males, 12-19%, females 13-20%

This test is not dependent upon exogenous organic or inorganic iodides. It is an indirect measure of thyroxin-binding protein which is of value in certain patients, e.g., in pregnancy when the PBI is falsely high due to increased thyroxin-binding while T<sub>3</sub> uptake is low. In general, T<sub>3</sub> uptake parallels the PBI.

This test is subject to many technical variables. It should be used only when the more standard tests do not give decisive information.

**Serum Cholesterol**  
Normal 150-280 mg /100 ml

**A Relatively Elevated** Myxedema R<sub>3</sub>-pothyroidism

**B Relatively Low** Thyrotoxicosis (occasionally)

This test is nonspecific as many factors may influence cholesterol level.

The absolute level is less significant than the change after institution of therapy.

### Serologic Tests.

Antibodies against several thyroid constituents may be found in the sera of patients with various types of thyroiditis (especially Hashimoto's disease) and, at times, in adenomatous goiters, in myxedema, and, rarely, in Graves' disease and thyroid carcinoma.

## SIMPLE GOITER

### Essentials of Diagnosis

- Enlarged thyroid gland in a patient living in an endemic area
- No symptoms except those associated with compression by large gland
- BMR, PBI, serum cholesterol normal; radioactive iodine uptake normal or elevated

It may be difficult in an anxious or nervous individual to distinguish from toxic goiter on clinical grounds alone. Single nodule suggests the possibility of neoplasm.

### General Considerations

Simple goiter is due to iodine lack, and occurs most commonly in endemic areas away from the seacoast. Relative insufficiency of the iodine leads to functional overactivity and hyperplasia of the gland, which becomes filled with colloid poor in iodine. If the deficiency is corrected, the enlargement may subside. In long-standing cases the goiter persists. Simple goiter may occur transiently when there is greater demand for thyroid hormone, e.g., with the onset of puberty or during pregnancy. Rarely, goiter may occur in spite of adequate iodine intake when there is interference with formation of thyroid hormones, e.g., due to excess intake of certain goitrogenic vegetables (rutabagas, turnips), exposure to thiocyanate, or congenital lack of certain enzyme systems. Goiter is more readily preventable than cured, and is less common since the introduction of iodized salt.



### Clinical Findings.

A. Symptoms and Signs: The gland is visibly enlarged and palpable. There may be no symptoms, or symptoms may occur as a result of compression of the structures in the neck or chest: wheezing, dysphagia, respiratory embarrassment (Note: Recurrent laryngeal compression is rare.)

B. Laboratory Findings: The BMR, PBI, and serum cholesterol are usually normal. The radioiodine uptake of the gland may be normal or high. Radioactive uptakes over nodules show them to be low in activity (in contrast to toxic nodular goiters).

With special techniques it is possible to demonstrate enzymatic defects in thyroid hormone production or abnormal circulating compounds. In a considerable number of patients with goiters, especially the familial types, Thyroid auto-antibodies may also be demonstrated.

### Differential Diagnosis.

It may be difficult to differentiate simple goiter from toxic diffuse or nodular goiter, especially in a patient with a great many nervous symptoms. A history of residence in an endemic area, a family history of goiter, or onset during stressful periods of life (e.g., puberty or pregnancy) will often help. If nodular, and especially if only a single nodule is present, neoplasm must be considered.

### Prevention.

With a dietary intake of 100-200 mcg of iodine daily, simple goiter should not occur. During times of stress (puberty, pregnancy, and lactation), the upper limits of this dose may be necessary. This amount is provided in 1-2 Gm. (15-30 gr.) of iodized salt daily.

### Treatment.

#### A. Specific Measures

1. Thyroid, 60-120 mg (1-2 gr) or more, or levothyroxine, 0.2 mg. or more, especially if the goiter is multinodular, appears to be of value in about half of cases. An excellent guide to therapy is the PBI, which should be maintained in the high normal range (6-7 mg./100 ml.). (Note: Misleadingly high blood iodine values may follow the use of iodized salt or diagnostic or therapeutic iodine-containing drugs.)

2. Iodine therapy (early) - If the enlargement is discovered early, it may disappear completely with adequate iodine administration. Five drops daily of saturated solution of potas-

sium iodide or strong iodine solution (Lugol's solution) in one-half glass water is sufficient. Continue therapy until the gland returns to normal size, and then place the patient on a maintenance dosage or use iodized table salt.

3. Iodine therapy (late) - If the enlargement is of long standing iodine therapy as above may be used, but significant regression in the size of the gland should not be expected. Note: Thyroid treatment is preferable in most patients with simple goiter.

#### B. Indications for Surgery:

1. Signs of pressure - If signs of local pressure are present, the gland should be removed surgically.

2. Potential malignancy - Surgery should be considered for any thyroid gland with a single nodule, for the chances of a single nodule being malignant are quite high. This is particularly true in younger people and in any case when there is no response to adequate thyroid after a period of 3-6 months.

### Prognosis

Simple goiter may disappear spontaneously or may become large, causing compression of vital structures. Multinodular goiters of long standing, especially in people over 50 years of age, may become toxic. Whether they ever become malignant is not established.

Astwood, E. B., Cassidy, C. E., & G. D.

Aurbach. Treatment of goiter and thyroid nodules with thyroid. J. A. M. A. 174 458-64, 1960.

## HYPOTHYROIDISM

In view of the profound influence exerted on all tissues of the body by thyroid hormone, lack of the hormone may affect virtually all body functions. The degree of severity ranges from mild and unrecognized hypothyroid states to striking myxedema.

A state of hypothyroidism may be due to primary disease of the thyroid gland itself, or lack of pituitary TSH. A true end-organ insensitivity to normal amounts of circulating hormone has been postulated but is rarely observed. Although gross forms of hypothyroidism, i.e., myxedema and cretinism, are readily recognized on clinical grounds alone, the far more common mild forms often escape detection without adequate laboratory facilities.

## 1 CRETINISM & JUVENILE HYPOTHYROIDISM

### Essentials of Diagnosis

- Dwarfism mental retardation dry yellow cold skin pot belly with umbilical hernia
- PBI low serum cholesterol elevated
- Delayed bone age stippling of epiphyses

Differentiate primary hypothyroidism from pituitary failure and from mongolism and other causes of stunted growth and skeletal development

### General Considerations

The causes of cretinism and juvenile hypothyroidism are as follows (after Wilkins)

#### A Congenital (Cretinism)

- 1 Thyroid gland absent or rudimentary (embryonic defect most cases of sporadic cretinism)
- 2 Thyroid gland present but defective in hormone secretion goitrous or secondarily atrophied Due to extrinsic factor (deficient iodine goitrogenic substances? most cases of endemic cretinism) or due to maternal factors (some cases of congenital goiter) Many cases are familial

#### B Acquired (Juvenile Hypothyroidism)

Atrophy of the gland or defective function may be due to unknown causes thyroiditis or operative removal (1 equal thyroid or toxic goiter) or secondary to pituitary deficiency

### Clinical Findings

**A Symptoms and Signs** All degrees of dwarfism may be seen with delayed skeletal maturation apathy physical and mental torpor dry skin with coarse dry brittle hair constipation slow teething poor appetite large tongue pot belly with umbilical hernia deep voice cold extremities and cold sensitivity and true myxedema of subcutaneous and other tissues A yellow carotenemic skin is not infrequent The thyroid gland is usually not palpable but a large goiter may be present which may be diffuse or nodular Sexual development is retarded but maturation eventually occurs Menometrorrhagia or amenorrhea may be seen in older girls Deafness is occasionally associated with goiters

**B Laboratory Findings** The BMR is probably the least reliable (in infants and children) and PBI the most reliable in sex of thy-

roid activity It is usually under 3 meg/100 ml Serum cholesterol is elevated Radioactive iodine uptake is very low in athyroid individuals but may be high in goitrous cretins although the iodine is not bound in the gland and is released By special techniques abnormal circulating iodine compounds and enzymatic defects in thyroid hormone production and release are demonstrable in some patients Others show circulating autoantibodies to thyroid constituents

### Differential Diagnosis

It is of practical interest to differentiate primary hypothyroidism from pituitary failure because in the latter instance a search for a pituitary lesion must be undertaken Treatment with thyroid hormone must be instituted cautiously when hypothyroidism is secondary to pituitary failure since it may precipitate adrenal crisis Radiiodine uptake studies before and after exogenous TSH administration will often show whether a gland is present or not True myxedema and hypercholesterolemia with hypopituitarism are rare Cretinism is most often confused with mongolism although retarded skeletal development is rare in mongoloid infants Macroglossia may be due to tumor e.g. lymphangioma The dry skin of ichthyosis may be misleading All causes of stunted growth and skeletal development (see below) must be considered as well Rather than risk the development of full blown cretinism in the questionable case a trial of thyroid therapy may be reasonable

### Treatment

See Myxedema p 519

### Prognosis

The progress and outcome of the disease depend largely upon the duration of thyroid deficiency and the adequacy and persistence of treatment Since mental development is at stake it is of utmost importance to start treatment early

The prognosis for full mental and physical maturation is much better if the onset is later in life Congenital cretins almost never attain full mental development Skeletal and sexual maturation though often retarded do take place normally under continued thyroid therapy

By and large the response to thyroid therapy is gratifying but therapy usually must be maintained throughout life

Stanbury JB & E M McGirr Sporadic or non endemic familial cretinism with goiter Am J Med 22 712 23 1957

## 2. ADULT HYPOTHYROIDISM & MYXEDEMA

### Essentials of Diagnosis

- Weakness, fatigue, cold intolerance, constipation, menorrhagia, hoarseness
- Dry, cold, yellow, puffy skin, scant eyebrows, thick tongue, "water bottle" heart, bradycardia, delayed return of deep tendon reflexes
- All low PBI, BMR, radiiodine uptake
- Anemia.

Differentiate between primary and secondary (pituitary lesion) types. In the latter, serum cholesterol and BP are normal or low. Hypothyroidism may present as a macrocytic anemia (differentiate from pernicious anemia), menstrual disorder (differentiate from primary pelvic disease), psychosis (myxedema madness), or intractable heart failure.

### General Considerations.

Primary thyroid deficiency is much more common than secondary hypofunction due to pituitary insufficiency. Primary myxedema occurs after total thyroidectomy, eradication of thyroid by radioactive iodine ingestion of goitrogens (e.g., thiocyanates, rutabagas), or chronic thyroiditis. Most cases, however, are due to atrophy of the gland from unknown causes, possibly an autoimmune mechanism.

Secondary hypothyroidism may follow destructive lesions of the pituitary gland, e.g., chromophobe adenoma or postpartum necrosis (Sheehan's syndrome). It is usually manifested by associated disorders of the adrenals and gonads. Since thyroid hormone is necessary for all glandular functions, primary myxedema may lead to secondary hypofunction of the pituitary, adrenals, and other glands, making diagnosis difficult.

### Clinical Findings.

These may vary from the rather rare full-blown myxedema to mild states of hypothyroidism, which are far more common and may escape detection unless a high index of suspicion is maintained.

#### A. Symptoms and Signs

1. Early - The principal symptoms are weakness, fatigue, cold intolerance, lethargy, dryness of skin, headache, and menorrhagia. Nervousness is a common finding. Physical findings may be few or absent. Outstanding

are thin, brittle nails, thinning of hair, which may be coarse, and pallor, with poor turgor of the mucosa. Delayed return of deep tendon reflexes is often found.

2. Late - The principal symptoms are slow speech, absence of sweating, weight gain, constipation, peripheral edema, pallor, hoarseness, aches and pains, dyspnea, anginal pain, deafness, and amenorrhea. Physical findings include puffiness of the face and eyelids, typical "malar flush," thinning of the outer halves of the eyebrows, thickening of the tongue, hard pitting edema, and effusions into the pleural, peritoneal, and pericardial cavities. Cardiac enlargement ("myxedema heart") is often due to pericardial effusion. Bradycardia and hypertension are also often present. Note: Obesity is not a common feature of hypothyroidism.

B. Laboratory Findings. A BMR below 30% is suggestive, especially in the nonobese patient. The PBI is under 3.5 mcg/100 ml. Radioiodine uptake is decreased (below 10% in 24 hours), but this test is not always reliable. The radioactive  $T_3$  uptake of the red cells is low (below 12%). Plasma cholesterol is elevated in primary but rarely in secondary hypothyroidism (fall on thyroid therapy is a sensitive index). Macrocytic anemia may be present. Increase in  $I^{131}$  uptake and PBI after administration of 10-20 units of thyrotropic hormone (given for several days) suggests secondary hypothyroidism rather than primary myxedema. 17-Ketosteroids may be very low.

### Differential Diagnosis

Mild hypothyroidism must be considered in all states of neurasthenia, menstrual disorders without grossly demonstrable pelvic disease, unexplained weight gain and anemia. Myxedema enters into the differential diagnosis of unexplained heart failure which does not respond to digitalis or diuretics, "idiopathic" hyperlipemia, and unexplained ascites. The protein content of myxedematous effusions is high. The thick tongue may be confused with that seen in primary amyloidosis. Pernicious anemia may be suggested by the pallor and the macrocytic type of anemia seen in myxedema. Some cases of primary psychosis and cerebral arteriosclerosis or even brain tumors must be differentiated from profound myxedema. (Note: The CSF proteins may be elevated in myxedema.) If laboratory tests are not convincing, response to cautious thyroid administration may establish the true nature of the disorder.

### Complications

Complications are mostly cardiac in nature, occurring as a result of advanced cor-

onary artery disease and congestive failure which may be precipitated by too vigorous thyroid therapy. There is an increased susceptibility to infection. Organic psychoses with paranoid delusions may occur ('myxedema madness'). Rarely adrenal crisis may be precipitated by thyroid therapy of pituitary myxedema.

**Caution.** Myxedematous patients are unusually sensitive to opiates and may die from average doses.

Refractory hyponatremia may be seen in severe myxedema.

## Treatment

**A. Specific Therapy.** Thyroid or a synthetic preparation is used. The initial dosage varies with the severity of the hypothyroidism.

**1. Caution.** When treating patients with severe myxedema or myxedema heart disease or elderly patients with hypothyroidism with other associated heart disease, begin with small doses of thyroid: 8-15 mg ( $\frac{1}{8}$ - $\frac{1}{4}$  gr.) daily for one week, and increase the dose every week by 15 mg ( $\frac{1}{4}$  gr.) daily up to a total of 100-200 mg ( $\frac{1}{2}$ -3 gr.) daily. This dosage should be continued until signs of hypothyroidism have vanished or toxic symptoms appear, and the dosage then stabilized to maintain the BMR or PBI at normal or just below the level of toxicity (see Hyperthyroidism below).

**2.** Patients with early hypothyroidism may be started with larger doses: 30 mg ( $\frac{1}{2}$  gr.) daily, increasing by 30 mg ( $\frac{1}{2}$  gr.) every week to the limit of tolerance.

**3. Maintenance.** Each patient's dose must be adjusted to obtain the optimal effect. Most patients require 60-200 mg (1-3 gr.) daily for maintenance. Optimal dosage can be estimated by following PBI or BMR, but clinical judgment is often the best guide.

**4.** Levothyroxine sodium (Synthroid®) is as good as thyroid.

**5.** When a rapid response is necessary, sodium liothyronine ( $T_3$ , Cytomel®) may be employed. Begin with very low doses because of its speed of action. Begin with 5 mcg and increase slowly (see p. 577). Note: The PBI cannot be used as a guide to  $T_3$  therapy.

## B. Needless Use of Thyroid

**1. Questionable diagnosis.** If any patient can tolerate above 200 mg (3 gr.) daily of thyroid, the diagnosis of hypothyroidism should be questioned. Normal individuals and obese and other nonhypothyroid individuals can tolerate doses up to 300-500 mg ( $4\frac{1}{2}$ -7 $\frac{1}{2}$  gr.) daily without changes in BMR or development of toxic symptoms.

**2. Nonspecific use of thyroid.** The use of thyroid medication as nonspecific stimulating

therapy is mentioned only to be condemned. It has been shown that the doses usually employed (100-200 mg) merely suppress the activity of the patient's own gland.

'Metabolic insufficiency' is a questionable entity. The empiric use of thyroid medication in cases of amenorrhea or infertility warrants further consideration.

## Prognosis

The patient may succumb to the complications of the disease if treatment is withheld too long. With early treatment, striking transformations take place both in appearance and mental function. Return to a normal state is possible, but relapses will occur if treatment is interrupted. On the whole, response to thyroid treatment is most satisfactory in true hypothyroidism, and complete rehabilitation of the patient is possible.

Ingbar S H & N Freinkel. Hypothyroidism. Disease A Month Year Book, Sept. 1958.

## HYPERTHYROIDISM (Thyrotoxicosis)

### Essentials of Diagnosis

- Weakness, sweating, weight loss, nervousness, loose bowel movements, heat intolerance.
- Tachycardia, warm, thin, soft moist skin, exophthalmos, stare, tremor.
- Goiter, bruit.
- BMR, PBI, radiolodine and radio- $T_3$ , red cell uptakes elevated.

Hyperthyroidism must be differentiated from anxiety neuroses, especially at the menopause. Hyperthyroidism may present as a refractory cardiac disease (e.g., failure, atrial fibrillation).

### General Considerations

Thyrotoxicosis is one of the most common endocrine disorders. Its highest incidence is in women between the ages of 20 and 40. When associated with ocular signs or ocular disturbances and a diffuse goiter, it is called Graves disease. This term, however, is commonly used to mean all forms of hyperthyroidism. Instead of a diffuse goiter, there may be a nodular toxic goiter, or all the metabolic features of thyrotoxicosis may be present without visible or palpable thyroid enlargement. The latter form is quite common in the elderly patient, who may even lack some of the hyper-

metabolic signs ("apathetic Graves' disease") but may present with a refractory cardiac illness. Lastly, a poorly understood syndrome of marked eye signs without hypermetabolism may follow treatment of thyrotoxicosis, and has been termed hyperexophthalmic Graves' disease, exophthalmic ophthalmoplegia, and malignant (progressive) exophthalmos.

#### Clinical Findings.

**A. Symptoms and Signs:** Restlessness, nervousness, irritability, easy fatigability, especially toward the latter part of the day, and unexplained weight loss in spite of ravenous appetite are often the early features. There is usually excessive sweating and heat intolerance, quick movements with incoordination varying from fine tremulousness to gross tremor. Less commonly, the patient's primary complaint is difficulty in focussing his eyes, pressure from the goiter, diarrhea, or rapid, irregular heart action.

The patient is quick in all motions, including speech. The skin is warm and moist and the hands tremble. A diffuse or nodular goiter may be seen or felt with a thrill or bruit over it. The eyes appear bright, there may be a stare, at times periorbital edema, and commonly lid lag, lack of accommodation, exophthalmos, and even diplopia. The hair and skin are thin and of silky texture. At times there is increased pigmentation of the skin, but vitiligo may also occur. Spider angiomas are common. Cardiovascular manifestations vary from tachycardia, especially during sleep, to paroxysmal atrial fibrillation and congestive failure of the "high-output" type. At times a harsh pulmonary systolic murmur is heard (Means' murmur). Lymphadenopathy and splenomegaly may be present. Wasting of muscle and bone (osteoporosis) are common features, especially in long-standing thyrotoxicosis. Rarely one finds nausea, vomiting, and even fever and jaundice (in which case the prognosis is poor). Mental changes are common, varying from mild exhilaration to delirium and exhaustion progressing to severe depression.

Associated with severe or malignant exophthalmos is at times a localized, bilateral, hard, nonpitting, symmetric swelling ("pretibial myxedema") over the tibia and dorsum of the feet. It often subsides spontaneously.

Thyroid "storm," rarely seen today, is an extreme form of thyrotoxicosis, which may occur after iodine refractoriness or thyroid surgery and is manifested by marked delirium, severe tachycardia, vomiting, diarrhea, and dehydration, and often very high fever. The mortality is high.

**B. Laboratory Findings:** The BMR is elevated, the PBI is over 8 mcg/100 ml., and radiolodine and radio-T<sub>3</sub> red cell uptakes are increased (the latter over 21%). In toxic nodular goiter a high radiolodine uptake in the nodule may be diagnostic if combined with elevated BMR and PBI. Serum cholesterol determinations are low (variable). Postprandial glycosuria is occasionally found. Urinary creatinine is increased. Lymphocytosis is common. Urinary and, at times, serum calcium are elevated.

**C. X-ray Findings:** Barium swallow may demonstrate low or intrathoracic goiter. Skeletal changes include diffuse demineralization or, at times, resorptive changes (osteitis).

**D. ECG Findings:** ECG may show tachycardia, atrial fibrillation, and P and T wave changes.

#### Differential Diagnosis.

The most difficult differentiation is between hyperthyroidism and anxiety neurosis, especially in the menopause. Acute or subacute thyroiditis may present with toxic symptoms, the gland is usually quite tender, and the thyroid antibody test may be positive (BMR is high, PBI may be elevated, but radiolodine uptake is very low). Exogenous thyroid administration will present the same laboratory features as thyroiditis.

Some states of hypermetabolism without thyrotoxicosis, notably severe anemia, leukemia, polycythemia, and malignancy, rarely cause confusion. Pheochromocytoma and acromegaly, however, may be associated with high BMR, with enlargement of the thyroid gland and profuse sweating, and make differentiation difficult.

Cardiac disease refractory to treatment with digitalis, quinidine, or diuretics suggests underlying hyperthyroidism. Other causes of ophthalmoplegia (e.g., myasthenia gravis) and exophthalmos (e.g., orbital tumor) must be considered. Thyrotoxicosis must also be considered in the differential diagnosis of muscle wasting diseases and diffuse bone atrophy. Diabetes mellitus and Addison's disease may coexist with thyrotoxicosis.

#### Complications.

The ocular and cardiac complications of long-standing thyrotoxicosis are most serious. Severe malnutrition and wasting with cachexia may become irreversible. If jaundice is present, the mortality increases. Thyroid "storm" (see p. 524) is rarely seen but may

be fatal. Malignancy almost never accompanies toxic goiter. Complications of treatment for goiter include drug reactions following iodine and thiouracil treatment, hypoparathyroidism and laryngeal palsy from surgical treatment and progressive exophthalmos. The exophthalmos may progress in the face of adequate therapy to the point of corneal ulceration and destruction of the globe unless orbital decompression is done. Hypercalcemia and nephrocalcinosis may be seen.

### Treatment

Treatment is aimed at halting excessive secretion of the thyroid hormone. Several methods are available; the method of choice is still being debated and varies with different patients. The most widely accepted method, however, is subtotal removal after adequate preparation.

**A Subtotal Thyroidectomy.** Adequate preparation is of the utmost importance. One or 2 drugs are generally necessary for adequate preparation: one of the thiouracil group of drugs alone or a thiouracil plus iodine.

**1 Thiouracil and similar drugs.** Several thiouracil drugs or similar derivatives are available: propylthiouracil, methylthiouracil, methimazole, and one containing iodine in the molecule, liothiouracil (Itrumil<sup>®</sup>). The modes of action of the first 3 are probably identical; the mode of action of liothiouracil is still not entirely clear, and this drug is of questionable value.

(1) Propylthiouracil has been most widely used and appears to be the least toxic. It is the thiouracil preparation of choice. When given in adequate dosage, propylthiouracil prevents the thyroid gland from transforming inorganic iodine into its organic (hormonal) form. This effect is very rapid (within a few hours) and continues as long as the drug is given. As the level of circulating hormone falls, TSH elaboration remains high. The BMR invariably falls, the rate of fall depending upon the total quantity of previously manufactured PBI available from the gland or in the circulating blood. (More PBI is present if iodine has previously been given.) The average time required for the BMR to return to normal is about 4-8 weeks. If the drug is continued, the BMR will continue to fall until the patient becomes myxedematous.

Propylthiouracil appears to be an ideal drug except for 2 disadvantages: the danger of toxic reactions (especially granulocytopenia) and interference with surgery. Toxic reactions to propylthiouracil are rare, however, and could be anticipated if the patient were

examined weekly and a weekly or a bi-weekly blood count taken, but this is rarely feasible. If the WBC falls below 4500 or if less than 45% granulocytes are present, therapy should be discontinued. Other rare reactions are drug fever, rash, and jaundice. The second objection is of a technical nature: since the gland may remain hyperplastic and vascular, surgical removal is more difficult. For this reason, combined therapy using propylthiouracil and iodine is probably the method of choice in preparing patients for thyroidectomy (see below).

Preparation is usually continued and surgery deferred until the BMR is normal. There is no need to rush surgery and no danger of escape, as with iodine. In severe cases, 100-200 mg, 4 times daily (spaced as close to every 6 hours as possible) is generally adequate. Larger doses (e.g., for patients with very large glands) are occasionally necessary. In milder cases, 100 mg t.i.d. are sufficient, although the larger doses are not more harmful.

(2) Methylthiouracil is almost the same as propylthiouracil in mode of action and dosage. Toxic reactions may be more frequent.

(3) Methimazole (Tapazole<sup>®</sup>) - The action of this drug is similar to that of the thiouracils. The average dose is 10-15 mg every 8 hours. The smaller dosage is no guarantee against toxic reactions, which are more common with this drug than with the thiouracils.

(4) Liothiouracil sodium (Itrumil<sup>®</sup>) is an iodinated thiouracil which is claimed to be nongonitrogenic. Although some favorable reports have been published, there have been reports of gradual escape while on the drug, as well as some cases of postoperative crisis. The dosage is 100-300 mg, 3-4 times daily.

**2 Iodine.** Iodine is given in daily dosages of 5-10 drops of strong iodine solution (Lugol's solution) or saturated solution of potassium iodide with nonspecific therapy (see below) until the BMR has dropped to about +20%; the signs and symptoms have become less marked and the patient has begun to gain weight. The disadvantages of preparation with iodine are that (1) a few patients may not respond, especially those who have received iodine recently; (2) if there is too long a wait before surgery, the gland may escape and the patient develops a more severe hyperthyroidism than before; and (3) it is generally impossible to reduce the BMR to normal with iodine alone.

**3 Combined propylthiouracil-iodine therapy.** - The advantage of this method is that one obtains the complete inhibition of thyroid secretion with the involuting effect of iodine. This can be done in 2 ways:

(1) Propylthiouracil followed by iodine - This appears at present to be the method of choice. Begin therapy with propylthiouracil, about 10-21 days before surgery is contemplated (usually when the BMR is about +10% or PBI < 8 mcg / 100 ml ), begin the iodine and continue for 1 week after surgery.

(2) Concomitant administration of the 2 drugs from the start in dosages as for the individual drugs, i.e., 100-200 mg propylthiouracil q i d and strong iodine solution, 10-15 drops daily.

**B Continuous Propylthiouracil Therapy (Medical Treatment)** Control of hyperthyroidism with propylthiouracil alone, without surgery, is advocated by some. The advantage is that it avoids the risks and postoperative complications of surgery e.g., myxedema, hypoparathyroidism. The disadvantage is the remote possibility of toxic reactions plus the necessity of watching the patient carefully for signs of hypothyroidism. Since the advent of propylthiouracil, it appears that the possibility of toxic reactions is slight.

Begin with 100-200 mg every 6-8 hours and continue until the PBI or BMR is normal and all signs and symptoms of the disease have subsided, then place the patient on a maintenance dose of 50-75 mg daily, observing the BMR or PBI frequently to avoid hypothyroidism.

An alternative method is to continue with doses of 50-200 mg every 6-8 hours until the patient becomes hypothyroid and then maintain BMR or PBI at normal with thyroid hormone (This may be the preferred treatment of exophthalmic goiter).

**Duration of therapy** - The duration of therapy and the recurrence rate with non-surgical therapy have not been completely worked out. At present it would seem that of the patients kept on propylthiouracil between 6 and 18 months (the dosage slowly decreased) about 50-70% will have no recurrence. Increasing the duration of therapy to about 2 years or more does not increase the "cure" rate.

**C Radioactive Iodine ( $I^{131}$ )** The administration of radioiodine has proved to be an excellent method for destruction of over-functioning thyroid tissue. The rationale of treatment is that the radioiodine, being concentrated in the thyroid, will destroy the cells that concentrate it. Because special techniques are necessary to measure and handle radioiodine, the method is still generally limited to use in medical centers. The only objections to date to radioiodine therapy are the possibility of

carcinogenesis and the possibility that an early carcinoma which might be removed surgically may remain undetected. For these reasons the use of radioiodine should generally be limited to older age groups (40 or above). Do not use this drug in pregnant women.

**D Continuous Iodine Therapy** In the past this method was used in selected cases of mild hyperthyroidism with fair results, however, because of the danger of "escape" and because propylthiouracil is a better drug, iodine should be used only for preoperative preparation.

**E X-ray therapy** has been used in skilled hands with good results as a substitute for surgery, but because of the time necessary to obtain full effect (3-6 months) this technique should be reserved for selected cases, it is rarely indicated when radioiodine is available.

#### F General Measures

1 The patient with hyperthyroidism should be at bed rest, especially in severe cases and in preparation for surgery. Mild cases may be treated with propylthiouracil on an ambulatory basis. However, early bed rest hastens recovery.

2 Diet should be high in calories, proteins, and vitamins. Hyperthyroid patients consume great quantities of food, are generally in negative nitrogen balance, and need the excess foods and vitamins because of their increased metabolic needs. Supplemental vitamin B complex should generally be employed.

3 Sedation - When first seen, these patients are often very nervous. Sedation is always helpful, and large doses, e.g., phenobarbital 30 mg (1/2 gr) 3-6 times daily, may be necessary. Reserpine in doses of 0.25 mg 2-3 times daily has been useful in many cases.

4 Testosterone propionate, 25-50 mg IM daily or 2-3 times/week, has been shown to be of value in restoring positive nitrogen balance, especially in debilitated patients. Do not use methyltestosterone, as this aggravates the creatinuria.

#### G Treatment of Complications

1 Exophthalmos - The exact cause of exophthalmos in hyperthyroidism is still not known. Although it may be due to excessive secretion of an anterior pituitary hormone which is different from TSH, the evidence is still inconclusive. It has been shown that exophthalmos is due to edema and later cellular infiltrations of the periorbital tissues. Removing the thyroid secretion (by extirpation or

administration of propylthiouracil) does not necessarily help this condition and may aggravate it leading to malignant exophthalmos. It has been suggested that this is because the thyroid secretion exerts an inhibitory effect on the anterior pituitary and removal of the gland allows the anterior pituitary to secrete more hormones and aggravate the condition. Some investigators believe that exophthalmos occurs with hyperthyroidism because the thyroid secretion in hyperthyroidism may be qualitatively abnormal and because this abnormal secretion does not have a depressant effect on the pituitary. Therefore it would seem rational to treat exophthalmos by giving thyroid orally.

(1) **Thyroid** - Immediately after surgery or after the PBI or BMR has returned to normal with propylthiouracil therapy begin giving thyroid 100-200 mg daily or levothyroxine sodium (Synthroid<sup>®</sup>) 0.1-0.3 mg daily. Give a dosage which is adequate to maintain the PBI at about 7-9 mg/100 ml. Although it is not always effective this therapy should be used whenever there is a tendency for progression of the exophthalmos.

(2) **Dark glasses** - protection from dust, eyes shields, tarsorrhaphy and other measures may be necessary to protect the eyes. Ophthalmologic consultation should be requested.

(3) **Corticotropin (ACTH)** or cortisones have proved helpful in some cases. They probably act by reducing the inflammatory reaction in the periorbital tissues.

(4) **Estrogen treatment** has been used with some benefit especially in the postmenopausal age group.

(5) **Surgery for malignant exophthalmos** - Every patient with exophthalmos should be measured periodically with an exophthalmometer. Do not rely upon clinical judgment to determine whether or not exophthalmos is present or progressing. In severe progressive cases where corneal edema, limitation of extraocular muscle movements and falling vision occur, orbital decompression is necessary to save the eyesight. There have been a few encouraging reports on the use of pituitary stalk section or even hypophysectomy with yttrium in severe malignant exophthalmos.

**2 Cardiac complications** - A number of cardiac complications are at times associated with hyperthyroidism.

(1) **Some degree of tachycardia** is always found if normal rhythm is present in thyrotoxicosis. This requires only the treatment of the thyrotoxicosis. Reserpine is at times helpful.

(2) **Congestive failure** tends to occur in long-standing thyrotoxicosis especially in the

older age groups. Treatment is the same as for congestive failure due to any cause. Digifalis seems to be effective in congestive failure associated with thyrotoxicosis.

(3) **Atrial fibrillation** may occur in association with thyrotoxicosis. Treat as any other atrial fibrillation but do not try to convert the atrial fibrillation in a toxic patient. Most cases will revert to normal rhythm soon after toxicity is removed. However if fibrillation remains for 2 weeks after surgery or for 2-4 weeks after BMR or PBI has returned to normal with propylthiouracil therapy and if no contraindications are present, one should consider using quinidine to convert to a normal rhythm.

**3 Crisis or storm** - Fortunately this condition is rare with modern therapy. It occurs now mainly in patients inadequately prepared with propylthiouracil and iodine immediately after subtotal thyroidectomy. It is characterized by high fever, tachycardia, CNS irritability and delirium. The cause is uncertain but absolute or relative adrenal cortical insufficiency may be important. Large doses of corticotropin (ACTH) and the cortisones may be lifesaving. Sodium iodide 1-2 Gm (15-30 gr) i.v. and repeated every 12-24 hours has also been advocated. Large doses of reserpine may be of value. General measures consist of cold packs and sedation.

### Prognosis

Thyrotoxicosis is a systemic disease and may subside spontaneously. More commonly however it progresses especially with recurrent psychic trauma, pregnancy and other types of stress. The ocular, cardiac and psychic complications often are more serious than the chronic wasting of tissues and may become irreversible even after treatment. Progressive exophthalmos is more common after surgical than after medical thyroidectomy. Hypoparathyroidism and vocal cord palsy are usually permanent after surgical thyroidectomy. With any form of therapy, recurrence rates are about 30%, especially if thyrotoxicosis is diffuse. With adequate treatment and long-term follow-up the results are good. It is perhaps wiser to speak of induced remission rather than cure. Post-treatment hypothyroidism is common.

Patients with jaundice and fever have a less favorable prognosis. Periorbital swelling and chemosis often precede serious and progressive malignant exophthalmos leading to blindness and must be watched carefully.

Although it is rare, thyroid storm has the worst prognosis. It is best avoided by careful preoperative preparation of the patient rather



than treated once it appears.

Dobyns, B. M.: Physiologic concepts in the diagnosis and treatment of Graves' disease. *Am. J. Med.* 20 684-97, 1956.

McCullagh, E. P.: Exophthalmos of Graves' disease: a summary of the present status of therapy. *Ann. Int. Med.* 48:445-70, 1958.

## CARCINOMA OF THYROID GLAND

### Essentials of Diagnosis.

- Painless swelling in region of thyroid, or thyroid nodule not responding to suppression.
- Normal thyroid function tests
- Past history of irradiation to neck, goiter, or thyroiditis.

Thyroid carcinoma must be differentiated from all types of functioning and nonfunctioning thyroid lesions

### General Considerations.

Although carcinoma of the thyroid is almost never associated with functional abnormalities, it enters into the differential diagnosis of all types of thyroid lesions. Recent evidence suggests that it may be the end result of long-standing overstimulation of the thyroid gland by pituitary TSH, especially in certain types of goiter and thyroiditis. It is common in all age groups, but especially in patients who have received irradiation therapy to the neck structures (e.g., thymus gland). The cell type determines to a large extent the type of therapy required and the prognosis for survival.

### Clinical Findings.

**A. Symptoms and Signs** The principal sign of thyroid cancer is a painless nodule, a hard nodule in an enlarged thyroid gland, so-called lateral aberrant thyroid tissue, or palpable lymph nodes with thyroid enlargement. Signs of pressure or invasion of the neck structures are present in anaplastic or longstanding tumors.

**B. Laboratory Findings** With very few exceptions all thyroid function tests are normal unless the disease is associated with thyroiditis. The scintigram shows a "cold nodule" which cannot be suppressed readily with  $T_3$  or  $T_4$ . Serum auto-antibodies are sometimes found.

**C. X-ray Findings** Extensive bone and soft tissue metastases (some of which may take up radiolodine) may be demonstrable.

### Differential Diagnosis.

Since nonmalignant enlargements of the thyroid gland are far more common than carcinoma, it is at times most difficult to establish the diagnosis except by biopsy (which should be an open biopsy rather than needle biopsy). The incidence of malignancy is much greater in single than in multinodular lesions, and far greater in nonfunctioning than in functioning nodules. The  $T_3$  suppression test is of some value in differentiating benign from autonomous lesions. The differentiation from chronic thyroiditis is at times most difficult, and the 2 lesions may occur together. Any nonfunctioning lesion in the region of the thyroid which does not decrease in size on thyroid therapy or increases rapidly must be considered carcinoma until proved otherwise.

Some Characteristics of Thyroid Cancer

	Papillary	Follicular	Amyloidic Solid	Anaplastic
Incidence* (%)	61	18	6	15
Average age*	42	50	50	57
Females* (%)	70	72	56	56
Deaths due to thyroid cancer* † (%)	6	24	33	98
Invasion: Juxtacapsular	+++++	+	+++++	+++
Blood vessels	+	+++	+++	+++++
Distant sites	+	+++	++	+++++
Resemblance to thyroid	+	+++	+	±
$^{131}\text{I}$ uptake	+	++++	+	0
Degree of malignancy	+	++ to +++	+++	+++++

\*Data based upon 885 cases analyzed by Woolner et al., and kindly supplied before publication, figures have been rounded to the nearest digit. [Reproduced, with permission, from Williams, Textbook of Endocrinology, 3rd Ed. Saunders, 1962.]

†Some patients have been followed up to 32 years after diagnosis.

### Complications

The complications vary with the type of carcinoma. Papillary tumors invade local structures such as lymph nodes. Follicular tumors metastasize through the blood stream. Anaplastic carcinomas invade local structures causing constriction and nerve palsies as well as leading to widespread metastases. The complications of radical neck surgery often include permanent hypoparathyroidism, vocal cord palsy, and myxedema.

### Treatment

Surgical removal if possible is the treatment of choice for most thyroid carcinomas. Papillary tumors may respond to thyroid suppressive treatment which may also be of value in other types (especially after most of the functioning gland has been removed). Some follicular tumors have been treated with radiolodine; metastases may take up radioactive iodine after thyroidectomy. External irradiation may be useful for local as well as distant metastases. Postoperative myxedema and hypoparathyroidism must be treated in the usual manner.

### Prognosis

The prognosis is apparently directly related to the cell type. The anaplastic carcinomas advance rapidly in spite of early diagnosis and treatment, while papillary tumors in spite of frequent bouts of recurrence are almost never fatal. In general the prognosis is less favorable in elderly patients.

Lindsay S. Carcinoma of the Thyroid Gland. Thomas, 1960.

Shands W C. Carcinoma of the thyroid in association with struma lymphomatosa. Ann Surg 151:6-58; 1960.

## THYROIDITIS

### Essentials of Diagnosis

- Painful swelling of thyroid gland causing pressure symptoms in acute and subacute forms and painless enlargement in chronic forms.
- Thyroid function tests variable; discrepancy in PBI and radiolodine uptake common.
- Serologic auto-antibody tests often positive.

Differentiate from all types of goiter especially if onset is rapid and

from inflammatory and neoplastic processes in the neck region.

### General Considerations

Thyroiditis has been more frequently diagnosed in recent years since special serologic tests for thyroid auto-antibodies became available. This heterogeneous group can be divided into two groups.

### Clinical Findings

#### A Symptoms and Signs

##### 1 Thyroiditis due to specific causes

(pyogenic infections, tuberculosis, syphilis). A rare disorder causing severe pain, tenderness, redness, and fluctuation in the region of the thyroid gland.

##### 2 Nonspecific (?auto-immune) thyroiditis

a Acute or subacute nonsuppurative thyroiditis (De Quervain's thyroiditis, granulomatous thyroiditis, giant cell thyroiditis, giant follicular thyroiditis). An acutely painful enlargement of the thyroid gland with dysphagia. The pain radiates into the ears. The manifestations may persist for several weeks and may be associated with signs of thyrotoxicosis and malaise. Middle-aged women are most commonly affected. Viral infection (perhaps mumps) has been suggested as the cause.

b Hashimoto's thyroiditis (struma lymphomatosa, lymphadenoid goiter, chronic lymphocytic thyroiditis). This is the most common form of thyroiditis and is seen principally in middle-aged women. Onset of enlargement of the thyroid gland is insidious with few pressure symptoms. Signs of thyroid dysfunction seldom appear but in a few cases the disease may progress to myxedema. The gland may show marked enlargement.

c Riedel's thyroiditis (chronic fibrous thyroiditis, Riedel's struma, woody thyroiditis, ligneous thyroiditis, invasive thyroiditis). This is the rarest form of thyroiditis and is found only in middle-aged women. Enlargement is often asymmetric; the gland is stone-hard and adherent to the neck structures causing signs of compression and invasion including dysphagia, dyspnea, and hoarseness.

#### B Laboratory Findings

BMR may be elevated in the early stages of acute and chronic thyroiditis and may be very low in the late stages of chronic thyroiditis. The PBI and  $T_3$  uptake of red cells are usually elevated in acute and subacute thyroiditis and normal or low in the chronic forms. Radioiodine uptake is characteristically very low in subacute thyroiditis. It may be high in chronic thyroiditis with enlargement of the gland and low in Riedel's struma. The TSH stimulation

test shows lack of response in most forms of thyroiditis. Leukocytosis, elevation of the sedimentation rate, and increase in serum globulins are common in acute and subacute forms. Thyroid auto-antibodies are most commonly demonstrable in Hashimoto's thyroiditis, but are also found in the other types.

#### Complications.

In the suppurative forms of thyroiditis any of the complications of infection may occur, the subacute and chronic forms of the disease are complicated by the effects of pressure on the neck structures, inanition, dyspnea, and, in Riedel's struma, vocal cord palsy. Many patients remain permanently myxedematous when the disease process subsides. Carcinoma may be associated with chronic thyroiditis and must be considered in the diagnosis of uneven painless enlargements which continue in spite of treatment.

#### Differential Diagnosis.

Thyroiditis must be considered in the differential diagnosis of all types of goiters, especially if enlargement is rapid. In the acute or subacute stages it may simulate thyrotoxicosis, and only a careful evaluation of several of the laboratory findings will point to the correct diagnosis. The very low radiiodine uptake in subacute thyroiditis with elevated *ESR* and a very rapid sedimentation rate is of the greatest help. Chronic thyroiditis, especially if the enlargement is uneven and if there is pressure and invasion of surrounding structures, may resemble carcinoma, and both disorders may be present in the same gland. The subacute and suppurative forms of thyroiditis may resemble any infectious process in or near the neck structures, and the presence of malaise, leukocytosis, and a high sedimentation rate is confusing. The thyroid auto-antibody tests have been of great help in the diagnosis of chronic thyroiditis, but the tests are not specific and may also be positive in patients with goiters, carcinoma, and occasionally even in thyrotoxicosis. Biopsy may be required at times to establish the diagnosis.

#### Treatment.

A. Suppurative Thyroiditis: Antibiotics, and surgical drainage when fluctuation is marked.

B. Subacute Thyroiditis: All treatment is empiric, and must be maintained for several

weeks since the recurrence rate is high. Corticotropin or corticoid treatment is often helpful, especially in the early stages. Salicylates in large doses (6-8 Gm./day) may be given for pain. Desiccated thyroid, 120-200 mg. (2-3 gr.), or thyroxin, 0.2-0.3 mg., may be helpful in shrinking the size of the gland after toxic symptoms have subsided. Low-dosage x-ray therapy (500-1200 r) is at times required if other measures fail. Propylthiouracil, 100-200 mg. every 8 hours, or methimazole, 20-40 mg. every 8 hours, may decrease tenderness.

Surgery is rarely required, splitting of the isthmus to relieve pressure and biopsy is the procedure of choice.

C. Hashimoto's Thyroiditis: Thyroid, thyroxin, or triiodothyronine in full doses often reduces the size of the gland markedly, since the disease will often progress to myxedema, this treatment probably should be continued indefinitely. Corticoid treatment often reduces the gland rapidly. X-ray therapy, propylthiouracil, and partial thyroidectomy are rarely required.

D. Riedel's struma often requires partial thyroidectomy to relieve pressure, adhesions to surrounding structures make this a difficult operation.

#### Prognosis.

The course of this group of diseases is quite variable. Spontaneous remissions and exacerbations are common in the subacute form, and therapy is nonspecific. The disease process may smolder for weeks. The chronic form may be part of a systemic collagen disease (e.g., lupus erythematosus, Sjögren's syndrome) with all of the complications of that disease. Recurrent subacute and, more often, chronic thyroiditis lead to permanent destruction of the thyroid gland in a large number of patients and to myxedema. Continuous thyroid replacement therapy, by suppressing TSH, may shrink the gland. It has also been suggested that this may lessen the tendency to malignant transformation in chronic thyroiditis.

Doniach, D., Hudson, R. V., & I. M. Roitt: Human auto-immune thyroiditis: clinical studies. *Brit. M. J.* 1:365-73, 1960.  
Steinberg, F. U.: Subacute granulomatous thyroiditis: a review. *Ann. Int. Med.* 52: 1014-25, 1960.

## THE PARATHYROIDS

### HYPOPARATHYROIDISM & PSEUDOHYPOPARATHYROIDISM

#### Essentials of Diagnosis

- Tetany carpopedal spasms stridor and wheezing muscle and abdominal cramps urinary frequency personality changes mental torpor
- Cataracts positive Chvostek's sign and Trousseau's phenomenon defective nails and teeth
- Serum calcium low serum phosphorus high alkaline phosphatase normal urine calcium (Sulkowitch) negative
- Basal ganglia calcification on x ray of skull

Differentiate from the tetany of respiratory or metabolic alkalosis (serum calcium normal) and tetany of early rickets and osteomalacia (serum phosphorus low). In chronic renal failure the serum chemistry is the same as in hypoparathyroidism but renal disease is usually evident (e.g. elevated NPN). Distinguish also from pseudohypoparathyroidism (insensitive to parathormone).

#### General Considerations

A deficiency of parathyroid hormone is most commonly seen following thyroidectomy or more rarely following surgery for parathyroid tumor. Very rarely it follows x ray irradiation to the neck or massive radioactive iodine administration for cancer of the thyroid.

Transient hypoparathyroidism may be seen in the neonatal period presumably due to a relative underactivity of the parathyroids or to extraordinary demands on the parathyroids by the intake of cow's milk containing a great deal of phosphorus. A similar mechanism may operate in the tetany of pregnancy.

Idiopathic hypoparathyroidism often associated with candidiasis may be familial and may be associated with Addison's disease. Pseudohypoparathyroidism is a genetic defect associated with short stature round face short metacarpals hypertension and ectopic bone formation. The parathyroids are present and often hyperplastic but the renal tubules do not respond to the hormone.

#### Clinical Findings

**A Symptoms and Signs** Acute hypoparathyroidism causes tetany with muscle cramps irritability carpopedal spasm and convulsions stridor wheezing dyspnea photophobia and diplopia abdominal cramps and urinary frequency. Symptoms of the chronic disease are lethargy personality changes anxiety state blurring of vision due to cataracts and mental retardation.

Chvostek's sign (facial contraction on tapping the facial nerve near the angle of the jaw) is positive and Trousseau's phenomenon (carpopedal spasm after application of a cuff) is present. Cataracts may occur the nails may be thin and brittle the skin dry and scaly at times with fungus infection (candidiasis) and loss of hair (eyebrows) and deep reflexes may be hyperactive. In pseudohypoparathyroidism the fingers and toes are short with absence of the knuckles of the fourth and fifth fingers on making a fist ectopic soft tissue calcification may be seen and felt. Choking of the optic disks is rarely found. Teeth may be defective if the onset of the disease occurs in childhood.

**B Laboratory Findings** Serum calcium is low serum phosphorus high urinary phosphorus low (TRP above 85%) urinary calcium low to absent (negative Sulkowitch test) and alkaline phosphatase normal. Alkaline phosphatase may be elevated in pseudohypoparathyroidism. NPN is normal.

**C X ray Findings** X rays of the skull may show basal ganglia calcifications the bones may be denser than normal (in pseudohypoparathyroidism short metacarpals and ectopic bone may be seen and bones may be demineralized).

**D Other Examinations** Slit lamp examination may show early cataract formation. EEG shows generalized dysrhythmia (partially reversible). ECG may show prolonged Q-T intervals.

#### Complications

These depend largely upon the duration of the disease and the age at onset. If it starts early in childhood there may be stunting of growth malformation of the teeth and retardation of mental development. In long standing cases cataract formation and calcification in the basal ganglia is seen. Permanent brain damage with convulsions may lead to admission to mental institutions. In addition there may be complications of overtreatment with calcium and vitamin D with renal impairment.

## Differential Diagnosis

The symptoms of hypocalcemic tetany are most commonly confused with or mistaken for tetany due to metabolic or respiratory alkalosis, in which the serum calcium is normal. Symptoms of anxiety are common in both instances, and fainting is not uncommon in the hyperventilation syndrome. The typical blood and urine findings should differentiate the 2 disorders. This holds true also for less common causes of hypocalcemic tetany, such as rickets and osteomalacia in the early stages. In this condition the serum phosphorus is invariably low or low normal, rarely high. Confusion might arise with the tetany due to chronic renal failure, in which retention of phosphorus will produce a high serum phosphorus with low serum calcium, but the differentiation should be obvious on clinical grounds (e.g., uremia, azotemia).

In primary aldosteronism with tetany (due to alkalosis) there is associated hypertension and hypokalemia with inability to concentrate the urine.

The physical signs of pseudohypoparathyroidism without the abnormal blood chemical findings are seen in certain dysplasias ("pseudopseudohypoparathyroidism").

In order to differentiate true hypoparathyroidism, which responds to parathyroid extract, from pseudohypoparathyroidism, which does not respond, the Ellsworth-Howard test (phosphaturia after administration of 200 units of parathormone I.V.) has to be performed. At times hypoparathyroidism is misdiagnosed as brain tumor (on the basis of brain calcifications, convulsions, choked disks), more rarely as "asthma" (on the basis of stridor and dyspnea). Other causes of cataracts and basal ganglia calcification also enter into the differential diagnosis.

## Treatment.

**A. Emergency Treatment for Acute Attack (Hypoparathyroid Tetany)** This usually occurs after surgery and requires immediate treatment.

1. Calcium chloride, 5-10 ml of 10% solution I.V., slowly until tetany ceases, or calcium gluconate, 10-20 ml of 10% solution I.V., may be given. Ten to 50 ml of either solution may be added to 1 L. of 5% glucose in water or saline and administered by slow I.V. drip. The rate should be so adjusted that hourly determination of urinary calcium by means of the Sulkowitch test will be positive.

2. Calcium salts should be given orally as soon as possible to supply 1-2 Gm. of calcium daily: calcium gluconate, 8 Gm. (2 tsp) t.i.d.; calcium lactate, 4-8 Gm. (1-2 tsp) t.i.d.; or calcium chloride, 2-4 Gm. (1/2-1

tsp) t.i.d. (as 30% solution)

3. Dihydroxyachysterol (Hytakerol<sup>®</sup>) or calciferol - Give dihydroxyachysterol as soon as oral calcium is begun. Begin with 4-10 ml. of oily solution (1.25 mg/ml) orally daily for 2-4 days, reduce dose to 1-2 ml daily for 1-3 weeks, and then determine maintenance requirements. The action of dihydroxyachysterol is irregular, and the drug is very expensive. Calciferol, 100,000-150,000 units (2-3 mg) daily, is just as effective and probably should be used in the majority of patients.

4. Parathyroid injection, 50-100 units I.M., or subcut 3-5 times daily as necessary to prevent tetany. Do not use parathyroid hormone for over one week. Use only as long as absolutely necessary. Actually, parathormone is rarely ever used, it is not very practical and usually not necessary.

## B. Maintenance Treatment

1. High-calcium, low-phosphorus diet (omit milk and cheese)

2. Calcium salts (as above except chloride) may be continued

3. Dihydroxyachysterol (Hytakerol<sup>®</sup>), 0.5-1 ml daily or 3 times weekly to maintain blood calcium at normal level

4. Calciferol, 50,000-200,000 units (1-3 mg) daily. In some cases up to 7 or 8 mg of calciferol daily may be substituted for dihydroxyachysterol. The vitamin D action is probably similar to that of dihydroxyachysterol, and it can certainly be substituted adequately clinically. The initial action of vitamin D appears to be slower. However, the cost to the patient is less than with dihydroxyachysterol, and the margin of safety is probably greater. It accumulates in the body over prolonged periods.

5. Aluminum hydroxide gel may be employed to help lower the serum phosphorus.

## Prognosis

The outlook is fair if prompt diagnosis is made and treatment instituted. Some changes (e.g., in the EEG) are reversible, but the cataracts and brain calcifications are permanent. They may be in part genetically determined and not related to hypocalcemia per se. Although treatment of the immediate acute attack is simple and effective, long-term therapy is tedious and expensive since a good preparation of parathormone is not available. Adequate control by a fairly intelligent patient is required to avoid undertreatment or overtreatment. Periodic blood chemical evaluation is required since sudden changes in blood levels may call for modification of the treatment schedule. The urinary calcium (Sulkowitch test) is of little value since hypercalciuria, regardless of blood calcium level,

Principal Findings in the Various Parathyroid Syndromes\*

Syndrome	Low Serum Ca With High Serum P	Serum Alkaline Phosphatase	Cataracts, Calcification of Basal Ganglia	Microdactylia Ectopic Bone	Subperiosteal Resorption (Osteitis)	Parathyroid Hyperplasia	Ellsworth-Howard Test
Hypoparathyroidism	+	Normal	+	0	0	0	+
Pseudohypoparathyroidism	+	Normal	+	+	0	+	0
Pseudo-pseudohypoparathyroidism	0	Normal	0	+	0	0	+
Secondary (renal) hyperparathyroidism	+	↑	0	0	+	+	±
Pseudohypoparathyroidism with secondary hyperparathyroidism	+	↑	±	+	+	+	0

\*Reproduced, with permission, from Kolb, F. O., & H. L. Steinbach. *J Clin Endocrinol* 22:68, 1962

†Responsiveness to parathyroid hormone

occurs with vitamin D therapy. Unrecognized or late cases may find their way into mental institutions.

Bronsky, D., & others. Idiopathic hypoparathyroidism and pseudohypoparathyroidism: case reports and review of the literature. *Medicine* 37:317-52, 1958.

## HYPERPARATHYROIDISM

### Essentials of Diagnosis

- Renal stones, nephrocalcinosis, polyuria, polydipsia, hypertension, uremia, intractable peptic ulcer
- Bone pain, cystic lesions and rarely pathologic fractures
- Serum and urine calcium elevated; urine phosphorus high with low to normal serum phosphorus; alkaline phosphatase normal to elevated
- "Band keratopathy" on slit lamp examination of eye
- X-ray subperiosteal resorption, loss of lamina dura of teeth, renal parenchymal calcification, bone cysts

The combination of biochemical findings noted above is almost pathognomonic of hyperparathyroidism; however, superimposed renal disease may confuse the picture (e.g., may give an elevated serum phosphorus). Certain cancers (e.g., lung, kidney, ovary) and multiple myeloma may rarely give similar chemical findings. Differenti-

ate from nonmetabolic bone disease and osteoporosis.

### General Considerations

While primary hyperparathyroidism is a relatively rare disease, it is potentially curable if detected early. It should always be suspected in obscure bone and renal disease, especially if calculi or nephrocalcinosis are present. Five percent of renal stones are associated with this disease.

Ninety percent of cases of primary hyperparathyroidism are caused by a single adenoma (or, in rare cases, 2 or more adenomas). Often familial, of the parathyroids, pancreas, and pituitary occur. 8% are caused by primary hypertrophy and hyperplasia of all 4 glands, and 2% are caused by carcinoma of one gland.

Secondary hyperparathyroidism is almost always associated with hyperplasia of all 4 glands; it is most commonly seen in chronic renal disease, but is also found in rickets and osteomalacia, pregnancy, and acromegaly.

Hyperparathyroidism causes excessive excretion of calcium and phosphorus by the kidneys; this produces eventually either diffuse parenchymal calcification (nephrocalcinosis) or calculus formation within the urinary tract (the 2 types rarely coexist). If the excessive demands for calcium are met by dietary intake (i.e., if the milk intake is adequate), the bones will not become drained (most common type in the United States). If milk intake is not adequate, bone disease occurs (so-called osteitis fibrosa cystica). Factors other than the calcium intake may determine whether bone disease will be present in hypoparathyroidism. This may show either diffuse demineralization.

pathologic fractures, or cystic bone lesions throughout the skeleton.

### Clinical Findings.

**A. Symptoms and Signs:** The manifestations of hyperparathyroidism may be divided into those referable to (1) skeletal involvement, (2) renal and urinary tract damage, and (3) hypercalcemia per se. Since the adenomas are small and deeply located, only about 5% of cases of adenoma can be demonstrated by barium swallow displacing the esophagus or by palpation of a mass in the neck. It may be associated with a thyroid adenoma or carcinoma.

**1 Skeletal manifestations** - These may vary from simple back pain, joint pains, painful shins, and similar complaints, to actual pathologic fractures of the spine, ribs, or

long bones, with loss of height and progressive kyphosis. At times an epulis of the jaw (actually a "brown tumor") may be the tell-tale sign of osteitis fibrosa. "Clubbing" of the fingers due to fracture and telescoping of the tips occur more rarely.

**2. Urinary tract manifestations** - Polyuria and polydipsia occur early in the disease. Sand, gravel, or stones containing calcium oxalate or phosphate may be passed in the urine. Secondary infection and obstruction may cause nephrocalcinosis and renal damage, leading eventually to uremia.

**3. Manifestations of hypercalcemia** - Thirst, nausea, anorexia, and vomiting are outstanding symptoms. Often one finds a past history of peptic ulcer, with obstruction or even hemorrhage. There may be stubborn constipation, asthenia, anemia, and weight loss.

Summary of Chemical Findings in Metabolic & Nonmetabolic Bone Disease\*

	Serum Calcium (mg./100 ml.)	Serum Phosphorus (mg./100 ml.)	Alkaline Phosphatase (Bodensky Units)	Urinary Calcium† (mg./24 hrs.)
Normal Adult	9-11	3-4 5	2-5	50-175
Metabolic				
Osteoporosis	Normal, rarely high	Normal	Normal	Normal or high
Osteomalacia	Low or normal	Low	High	Low if absorptive defect, high if renal defect.
Osteitis fibrosa cystica				
Primary hyperparathyroidism	High	Low	High	High
Secondary hyperparathyroidism	Low or normal	High	High	Low, normal or high
Nonmetabolic				
Paget's disease	Normal or high	Normal	High	Normal or high
Multiple myeloma	Normal or high	Normal (rarely high or low)	Normal or high	Normal or high
Metastatic malignancy	Normal or high	Normal (or rarely low)	Normal or high	Normal or high

\*Reproduced, with permission, from Felix O. Kolb, *Metabolic Diseases of Bone in the Adult*, Kaiser Foundation Medical Bulletin 4:351, 1956.

†Urinary calcium on a diet free of milk and cheese and their products. Instead of a quantitative test, spot checks with Sulkowitch reagent are informative. (Use equal amounts, about 5 ml. each of urine and reagent.)

Reading: 0 = No cloud

1+ = Faint cloud after several seconds

2+ = Faint cloud appearing immediately

Normal patients have 1-2+ urine depending upon urine volume.

3+ = Dense cloud without flocculation

4+ = Heavy flocculation

Depression and psychosis may occur. Of unusual interest is hypermotility of joints. The fingernails and toenails may be unusually strong and thick. Calcium may precipitate in the eyes ("band keratopathy"). In secondary (renal) hyperparathyroidism, calcium also precipitates in the soft tissues, especially around the joints. Recurrent pancreatitis occurs in some patients.

**B Laboratory Findings** Serum calcium is usually high (adjust for serum protein), the serum phosphorus is low or normal, the urinary calcium is often high, there is an excessive loss of phosphorus in the urine in the presence of low to low normal serum phosphorus (low tubular reabsorption of phosphate, TRP below 80-90%), the alkaline phosphatase is elevated only if bone disease is present. (In secondary hyperparathyroidism the serum phosphorus is high as a result of renal retention, and the calcium is low or normal.)

**C. X-ray Findings** X-ray rarely demonstrates the tumor on barium swallow, if bone disease is present, one may see diffuse demineralization, subperiosteal resorption of bone (especially in the radial aspects of the fingers), and often loss of the lamina dura of the teeth. There may be cysts throughout the skeleton, mottling of the skull ("salt and pepper appearance"), or pathologic fractures. One may find diffuse stippled calcifications in the region of the kidneys (nephrocalcinosis) or calculi in the urinary tract. Soft tissue calcifications around the joints and in the blood vessels may be seen in renal osteitis.

**D. ECG** may show a shortened Q-T interval.

**E. Slit lamp examination** of the eye may show corneal calcification ("band keratopathy").

### Complications

Although the striking complications are those associated with skeletal damage (e.g., pathologic fractures), the serious ones are those referable to renal damage. Urinary infection due to stone and obstruction may lead to renal failure and uremia. If the serum calcium level rises rapidly (e.g., due to dehydration or salt restriction), "parathyroid poisoning" may occur, with acute renal failure and rapid precipitation of calcium throughout the soft tissues (hyperparathyroidism). Peptic ulcer and pancreatitis may be intractable before surgery. Pancreatic islet cell adenoma with hypoglycemia may be associated, or ulcerogenic pancreatic tumor may coexist. Hypertension is frequently found.

**Differential Diagnosis.** (See chart on p. 456.)

If chemical determinations are reliable, the combination of high calcium and low phosphorus in the serum, high urinary phosphorus and calcium, and normal or high alkaline phosphatase is almost pathognomonic of hyperparathyroidism. Only rarely has this combination been seen in multiple myeloma, metastatic cancer (kidney, bladder, thyroid), and hyperthyroidism. If renal damage is present, the typical picture may be obscured, i.e., the serum phosphorus may not be low. Other causes of hypercalcemia (e.g., sarcoidosis, vitamin D intoxication) will respond to the administration of cortisone (cortisone test), which usually does not affect the hypercalcemia of primary hyperparathyroidism. If bone disease is present, the typical subperiosteal resorption may differentiate osteitis fibrosa from nonmetabolic bone disease and from osteoporosis. Bone biopsy may at times settle the diagnosis.

Recently, nonmetastasizing carcinomas (e.g., of the lung, kidney, or ovary) have been described with blood chemical changes identical with those seen in hyperparathyroidism; these changes are reversible upon removal of these tumors.

### Treatment.

**A. Surgical Measures.** If a parathyroid tumor, the usual cause, is found, it should be removed surgically. The surgeon must be aware that multiple tumors may be present, the tumor may be in an ectopic site, e.g., the mediastinum. Hyperplasia of all glands requires removal of 3 glands and subtotal resection of the fourth before cure is assured. Caution. After surgery the patient may in the course of several hours develop tetany (sometimes transient) as a result of rapid fall of blood calcium even though the calcium level may fall only to the normal or low normal range. Therapy is as for hypoparathyroid tetany (see p. 529).

**B. Fluids.** A large fluid intake is necessary so that a diluted urine will be excreted to minimize the formation of calcium phosphate renal stones.

**C. Treatment of Hypercalcemia.** Force fluids, mobilize the patient, reduce calcium intake, and consider a trial of corticoid in large doses, both orally and parenterally, or of sodium phytate (Rencal®), 3 Gm. t.i.d. orally. Note: The patient with hypercalcemia is very sensitive to the toxic effects of digitalis.

### Prognosis.

The disease is usually a chronic progressive one unless treated successfully by surgical removal.



Spontaneous improvement due to necrosis of the tumor has been reported but is exceedingly rare. The prognosis is directly related to the degree of renal impairment. The bones, in spite of severe cyst formation, deformity, and fracture, will heal completely if a tumor is successfully removed. Once significant renal damage has occurred, however, it progresses even after removal of an adenoma, and life expectancy is materially reduced. Secondary hyperparathyroidism not infrequently results due to irreversible renal impairment. In carcinoma of the parathyroid (rare) the prognosis is hopeless. If hypercalcemia is severe, the patient may suddenly die in cardiac arrest or may develop irreversible acute renal failure.

Chambers, E. L., & others: Tests for hyperparathyroidism: tubular reabsorption of phosphate, phosphate deprivation and calcium infusion. *J. Clin. Endocrinol.* 16:1507-21, 1956.

Thomas, W. C., Jr., Connor, T. B., & H. G. Morgan: Diagnostic considerations in hypercalcemia with a discussion of the various means by which such a state may develop. *New England J. Med.* 260:591-6, 1959.

## METABOLIC BONE DISEASE

### OSTEOMALACIA & RICKETS

#### Essentials of Diagnosis

- Muscular weakness, listlessness
- Aching and "bowing" of bones
- Serum calcium low to normal, serum phosphorus low, alkaline phosphatase elevated.
- "Pseudofractures" and "washed out" bone on x-ray.

The acute form of osteomalacia and rickets, with tetany, must be differentiated from other causes of tetany (e.g. hypoparathyroidism). The disorders of malabsorption leading to osteomalacia must be differentiated from renal tubular disorders, since management and prognosis differ.

#### General Considerations.

Osteomalacia is the adult form of rickets. It is a condition resulting from a calcium and phosphorus deficiency in the bone. It may be caused by insufficient absorption from the in-

testine, due either to a lack of calcium alone, or a lack of or resistance to the action of vitamin D. In adults, this form of osteomalacia is almost always found in association with disorders of fat absorption (diarrhea, sprue, pancreatitis). The other more common variety of osteomalacia is found in association with renal calcium and/or phosphorus losses ("vitamin D-resistant rickets"). This is often a familial disorder. It is found in tubular disorders, either tubular "leaks" of phosphorus and calcium due to failure of reabsorption, or due to excessive losses associated with tubular acidosis (calcium dissolved out of the bone to spare sodium or potassium, or both). There may be associated glycosuria and aminoaciduria (Fanconi's syndrome).

Almost all forms of osteomalacia are associated with compensatory, secondary hyperparathyroidism, set off by the low calcium level. It is for this reason that most patients will show only slightly low serum calcium levels (compensated osteomalacia).

A special form of osteomalacia is the so-called Milkman's syndrome, an x-ray diagnosis of multiple, bilaterally symmetric pseudofractures which may represent the shadows of blood vessels traversing and eroding the soft skeleton. Rickets, which is the counterpart of osteomalacia in the growing child, shows additional features, especially around the epiphyses, which are "motheaten" on x-ray. There is also beading of the ribs, Harrison's groove, bowlegs, and disturbances in growth.

In contrast to osteoporosis, where fractures are more common, osteomalacia is more often associated with bowing of bones.

#### Clinical Findings.

A. Symptoms and Signs. Manifestations are variable, ranging from almost none in mild cases to marked muscular weakness and listlessness in advanced cases. There is usually mild aching of the bones, and a tendency to bowing. In the very early and acute osteomalacias a rapidly falling calcium level may be associated with clinical tetany, although this is rare. As compensation takes place, tetanic features are absent. In states of deficient absorption, other features of the sprue syndrome, such as glossy tongue or anemia, may be present. A low potassium syndrome with muscular weakness and paralysis may be present with renal tubular disorders.

B. Laboratory Findings. Serum calcium is low or normal, but never high. Serum phosphorus is low (may be normal in early stages). The alkaline phosphatase is elevated except in the early phase. Urinary calcium

and phosphorus are very low in absorption disorders or high in renal lesions. X-rays show involvement of the pelvis and long bones, with demineralization and bowing, less often, the spine and skull are involved as well. Fractures are rare except for "pseudofractures". The I.V. calcium infusion test demonstrates avidity of bone for calcium (80-90% retained) in osteomalacia due to malabsorption. Laboratory findings of the primary steatorrhea or renal disease may be present. In renal tubular acidosis the serum  $\text{CO}_2$  is low and the serum chloride level is elevated, the serum potassium may be very low, the urinary pH is fixed near the alkaline side. Glycosuria and aminoaciduria are found in the Fanconi syndrome.

### Differential Diagnosis

It is most important to recognize osteomalacia and consider it in the differential diagnosis of bone disease since it is a potentially curable disease. The childhood forms may be mistaken for osteogenesis imperfecta or other nonmetabolic bone disorders.

The acute forms must be differentiated from other forms of tetany. The long-standing disease enters into the differential diagnosis of any metabolic or generalized nonmetabolic bone disease (see table on p. 531). The pseudofracture is often the outstanding sign of latent osteomalacia. Osteoporosis may exist as well, and may obscure the osteomalacia. At times the diagnosis is confirmed by a rise of phosphatase after treatment with vitamin D and calcium. Renal tubular acidosis is a cause of nephrocalcinosis, and must be considered in the differential diagnosis of kidney calcifications with bone disease such as hyperparathyroidism. The joint aches and pains may be mistaken for some form of arthritis.

### Treatment.

#### A. Specific Measures

1. Rickets - Vitamin D, even in small doses, is specific, 2000-5000 units daily are adequate.

2. Adult osteomalacia and Milkman's syndrome - Vitamin D is specific but very large doses are necessary to compensate for renal losses of phosphate. Give until an effect is noted on the blood calcium. The usual dose is 25-100 thousand units daily. Doses up to 300,000 units or more daily may be necessary, but if the doses are over 100,000 daily, they must be used cautiously with periodic determinations of serum and urine calcium, the serum phosphorus may remain low.

3. Pancreatic insufficiency - Adequate replacement therapy is of paramount importance. High calcium intake and vitamin D,

50-150 thousand units daily, are also of value.

4. Sprue syndrome - Folic acid and vitamin  $\text{B}_{12}$  appear to be of value.

5. Some rare forms of renal disease - Treatment is aimed at the altered renal physiology, e.g., alkali therapy in renal tubular acidosis, potassium replacement.

B. General Measures. High-calcium diet and calcium gluconate or calcium lactate 4-20 Gm (1-5 tsp) daily.

### Prognosis

The prognosis is usually excellent in the absorptive disorders if diagnosed early. This does not hold for certain of the vitamin D-resistant forms of osteomalacia or rickets or for Fanconi's disease, which respond slowly or not at all unless huge amounts of vitamin D are given. Hypercalcemia may occur as a complication of therapy. In the renal forms the ultimate prognosis is that of the basic kidney disease. Respiratory paralysis due to hypokalemia may prove fatal.

## OSTEOPOROSIS

### Essentials of Diagnosis

- Asymptomatic to severe backache
- Spontaneous fractures and collapse of vertebrae without spinal cord compression, often discovered "accidentally" on x-ray.
- Loss of height
- Calcium, phosphorus, and alkaline phosphatase normal
- Demineralization of spine and pelvis

Osteoporosis must be differentiated from other metabolic bone disease especially osteomalacia (similar x-ray picture) and hyperparathyroidism. The x-rays of multiple myeloma patients may show only diffuse demineralization. Metastatic bone disease must also be differentiated, since it may be aggravated by hormonal therapy and may coexist in the postmenopausal patient.

### General Considerations

Osteoporosis is the most commonly seen metabolic bone disease in the United States. It is primarily a disorder of the bone matrix. Absence of bone matrix leads to demineralization of the skeleton because the lime salts cannot precipitate on the matrix and because osteoblastic activity is not present.

### A Principal Causes

1 Lack of activity, e.g., immobilization as in paraplegia or rheumatoid arthritis (Osteoblasts depend upon strains and stresses for proper function)

2 Lack of estrogens ("postmenopausal osteoporosis") (Females are deprived of estrogens relatively early in life. About 30% of women over 60 years of age have clinical osteoporosis. Some degree of osteoporosis is almost always present in senility)

### B Less Common Causes

1 Developmental disturbances (e.g., osteogenesis imperfecta)

2 Nutritional disturbances (e.g., protein starvation and ascorbic acid deficiency)

3 Chronic calcium depletion is claimed by some investigators to cause osteoporosis

4 Endocrine diseases - Lack of androgens (eunuchoidism, senility in men) hypopituitarism (causes secondary gonadal failure), acromegaly (cause unknown, possibly due to hypogonadism), thyrotoxicosis (not constant causes excessive catabolism of protein tissue) excessive exogenous or endogenous ACTH or corticoids causing catabolism of bone (e.g., Cushing's disease) and long-standing uncontrolled diabetes mellitus (rare)

5 Bone marrow disorders - The presence of abnormal cells in the bone marrow such as in myeloma or leukemia, may prevent osteoblastic activity and cause osteoporosis. This is in addition to the active replacement of the marrow with tumor cells

6 Idiopathic osteoporosis - The cause is undetermined. It is most common in young men and women but occasionally occurs in older people, and does not respond well to therapy

C. Laboratory Findings Serum calcium, phosphorus, and alkaline phosphatase are normal. Urinary calcium is high early, normal in chronic forms

D X-ray Findings X-ray shows compression of vertebrae. The principal areas of demineralization are the spine and pelvis, demineralization is less marked in the skull and extremities. The lamina dura is preserved. Kidney stones may be seen in acute osteoporosis

### Differential Diagnosis

It is important not to confuse this condition with other metabolic bone diseases, especially osteomalacia and hyperparathyroidism, or with myeloma and metastatic bone disease especially of the breast and uterus, since estrogen therapy may aggravate them (see chart on p 531). Bone biopsy may be required

A rare case of hypophosphatasia may appear as "osteoporosis"

### Treatment.

A Specific Measures Specific treatment varies with the cause, but combined hormone therapy is usually indicated

1 Postclimacteric (mostly in females) - Estrogens may be of value in stimulating osteoblasts. Before beginning estrogen therapy in pelvic examination to rule out neoplasm or other abnormality and warn the patient or a relative that vaginal bleeding may occur. Administer estrogen daily except for the first 5-7 calendar days of each month and then repeat the cycle. Any of the following may be used: (1) Diethylstilbestrol, 0.5-2 mg orally daily as tolerated. (2) Ethinyl estradiol, 0.02-0.05 mg orally daily as tolerated. (3) Estrone sulfate, 1.25-2.5 mg orally daily

Testosterone may be used in addition to estrogen for its protein anabolic effect and hence its tendency to lay down bone matrix. Give methyltestosterone 5-10 mg orally daily. Avoid overdosage in females since excessive use may cause the appearance of male secondary sex characteristics. However, these usually regress if therapy is stopped. Some of the newer anabolic agents, e.g., estradiol valerate and testosterone (Deladumone<sup>®</sup>), norethandrolone (Nilevar<sup>®</sup>), or methandrostenolone (Dianabol<sup>®</sup>), may be used (see p 581)

2 Old age and idiopathic - As for postclimacteric, both testosterone and estrogens should be used in both males and females. Use with caution in very old people

3 Patients with malnutrition - Adequate diet is of great importance. However, hormones may be used as above if response to diet alone is poor

4 Cushing's disease - See p 542

B General Measures The diet should be high in protein and adequate in calcium (milk and milk products are desirable). If the patient is malnourished or if osteomalacia is present also give a high-calcium intake and vitamin supplementation, including vitamin D, 2000-5000 units daily. Patients should be kept active, bedridden patients should be given active or passive exercises, and calcium intake must be restricted

### Prognosis

With proper and prolonged therapy the prognosis is good for postclimacteric osteoporosis. Spinal involvement is not reversible on x-ray, but progression of the disease is halted. In general, osteoporosis is a crippling

rather than a killing disease and the prognosis is essentially that of the underlying disorder (e.g. Cushing's disease). The idiopathic variety does not respond appreciably to any form of therapy. Careful periodic records of patient's height will indicate if the disease process has become stabilized.

- Albright F & E C Reifenstein. The Parathyroid Glands and Metabolic Bone Disease. Williams & Wilkins. 1948.
- Henneman P H & S Wallach. The use of androgens and estrogens and their metabolic effects. Symposium. A review of the prolonged use of estrogens and androgens in postmenopausal and senile osteoporosis. Arch Int Med 100 715 23 1957.

## NONMETABOLIC BONE DISEASE

(See Table on p. 531)

### POLYOSTOTIC FIBROUS DYSPLASIA (Osteitis Fibrosa Disseminata)

#### Essentials of Diagnosis

- Painless swelling of involved bone or fracture with minimal trauma; brown skin pigmentation with ragged borders may be present.
- Bone cysts (may be hyperostotic) usually multiple but occasionally single in segmental distribution.
- Precocious puberty may occur in females.
- Serum calcium and phosphorus normal; alkaline phosphatase elevated.

Must be differentiated from the bone lesions (cysts, fractures) of hyperparathyroidism and neurofibromatosis. Hyperostotic lesions must be distinguished from Paget's disease and from bone tumors.

#### General Considerations

Polyostotic fibrous dysplasia is a rare disease which is frequently mistaken for osteitis fibrosa generalisata due to hyperparathyroidism since both are manifested by bone cysts, fractures and other findings. Polyostotic fibrous dysplasia is not a metabolic disorder of bone but a congenital dysplasia in

which bone and cartilage do not form but remain as fibrous tissue.

Polyostotic fibrous dysplasia which is associated with 'brown spots' with ragged margins and with true precocious puberty in the female is called Albright's syndrome. Hyperthyroidism may be present also.

#### Clinical Findings

**A. Symptoms and Signs.** The manifestations are painless swelling of the involved bone (usually the skull, upper end of femur, tibia, metatarsals, metacarpals, phalanges, ribs and pelvis) either singly or in multiple distribution with cysts or hyperostotic lesions and at times with brown pigmentation of the overlying skin. Involvement is segmental and may be unilateral. True sexual precocity may occur in females with early development of secondary sex characteristics and rapid skeletal growth.

**B. Laboratory Findings.** Calcium and phosphorus are normal; the alkaline phosphatase may be slightly elevated.

**C. X-ray Findings.** X-rays reveal rarefaction and expansion of the affected bones or hyperostosis (especially of base of the skull). Fractures and deformities may also be visible.

#### Differential Diagnosis

The bone cysts and fractures should be distinguished from those of hyperparathyroidism and neurofibromatosis. All other types of bone cyst and tumor must be considered also. The hyperostotic lesions of the skull must be distinguished from those of Paget's disease. Biopsy of bone may be required to settle the diagnosis.

#### Complications

Shortening of the extremity or deformity (e.g. shepherd's crook deformity of femur) may follow extensive involvement of bone.

#### Treatment

There is no treatment except for surgical correction of deformities, e.g. fractures, expanding cyst in the orbit.

#### Prognosis

Most lesions heal and the progression is slow. Since precocity is of the isosexual type, girls are susceptible to early pregnancy. They will ultimately be of short stature.

## PAGET'S DISEASE (Osteitis Deformans)

### Essentials of Diagnosis.

- Often asymptomatic. Bone pain may be the first symptom.
- Kyphosis, bowed tibias, large head, waddling gait, and frequent fractures which vary with location of process.
- Serum calcium and phosphorus normal; alkaline phosphatase elevated.
- Dense, expanded bones on x-ray.

Differentiate from primary bone lesions such as osteogenic sarcoma or multiple myeloma, and secondary bone lesions such as metastatic carcinoma and osteitis fibrosa cystica

### General Considerations.

Paget's disease is a nonmetabolic bone disease of unknown etiology which causes excessive bone destruction and repair, with associated deformities since the repair takes place in an unorganized fashion. Up to 3% of persons over age 50 will show isolated lesions, but clinically important disease is much less common.

### Clinical Findings.

**A. Symptoms and Signs.** Often mild or asymptomatic. Deep "bone pain" is usually the first symptom. The bones become soft, leading to bowed tibias, kyphosis, and frequent fractures with slight trauma. The head becomes large, and headaches are a prominent symptom. Increased vascularity over the involved bones causes increased warmth.

**B. Laboratory Findings.** The blood calcium and phosphorus are normal, but the alkaline phosphatase is markedly elevated.

**C. X-ray Findings.** On x-ray the involved bones are expanded and denser than normal. The initial lesion may be destructive and radiolucent.

### Complications.

Fractures are frequent and occur with minimal trauma. If immobilization takes place and there is an excessive milk intake, hypercalcemia and kidney stones may develop. Bony overgrowth may impinge on vital structures, especially nerves, causing deafness and blindness. Long-standing cases may progress to osteosarcoma. The increased vascularity, acting as multiple arteriovenous fistulas, may give rise to high-output cardiac failure.

### Treatment.

Supply a high-protein diet with adequate vitamin C intake. A high-calcium intake is desirable also unless the patient is immobilized, in which case calcium must be restricted. Vitamin D, 50,000 units 3 times a week, is helpful in some patients. Anabolic hormones, e.g., estradiol valerate and testosterone (Deladumone<sup>®</sup>), 1-3 ml./month, should be given as for osteoporosis. Corticosteroid treatment relieves pain but aggravates coexisting osteoporosis. Salicylates in large doses have recently been claimed to be useful in combating pain and reducing hypercalciuria.

### Prognosis.

The prognosis of the mild form is good, but sarcomatous changes (in 1-3%) or renal complications secondary to hypercalciuria (in 10%) alter the prognosis unfavorably. In general, the prognosis is worse the earlier in life the disease starts. Fractures usually heal well. In the severe forms, marked deformity, intractable pain, and cardiac failure are found.

Kolb, F.O.: Paget's disease. *California Med.* 91:245-50, 1959

## DISEASES OF THE ADRENAL CORTEX

Total destruction of both adrenal cortices is not compatible with human life. The cortex regulates a variety of metabolic processes by means of secretion of some 30 steroid hormones.

The stimulus for release of steroid hormones from the adrenal cortex - with the possible exception of aldosterone - appears to be adrenocorticotrophic hormone (ACTH) from the anterior pituitary which, in turn, is probably under hypothalamic control. Clinical syndromes of adrenal insufficiency or excess may thus be due to primary lesions of the adrenal glands themselves or may be secondary to pituitary disorders. Although the differentiation is often important from the diagnostic standpoint, treatment is usually directed toward the cortical disorder itself, whether primary or secondary. Many of the steroids isolated from the adrenal cortex are not active, and some have more than one action. In general, the adrenocortical hormones have 3 types of activity:

(1) Anabolic (Sex Steroids) Androsterone and related steroids are protein builders and are also virilizing and androgenic, and rep-

resert the principal source of androgens in the female. This group also includes adrenal estrogens and progesterone like steroids but these are of lesser clinical importance.

(2) Antianabolic or Catabolic (Glucocorticoids) Hydrocortisone, cortisone and related steroids the stress hormones of the adrenal cortex are vital for survival. They are glycostatic and cause gluconeogenesis from protein. They also play a role in potassium and water diuresis. Increased production or administration of large doses causes increased fat deposition in special sites (face buffalo hump), raises BP and causes eosinopenia and lymphopenia.

(3) Electrolyte regulating (mineralocorticoids) The principal hormone in this group is aldosterone. Its primary role is in retaining sodium and excreting potassium and thus regulating the extracellular fluid compartment and the BP. It has minor effects on carbohydrate metabolism.

Most of the clinical features of both adrenal insufficiency and excess can be explained on the basis of the above types of activity. Since mixed pictures occur, however, and since excess of 1 type of activity may coexist with deficiency of another (e.g. congenital adrenal virilism), exact physiologic correlation is difficult. Some phenomena, e.g. the pigmentation of adrenal insufficiency, are not yet fully explained and may be due to a pituitary intermediate or ACTH excess.

- Forsham P H. The adrenals. Chap 5 in Textbook of Endocrinology 3rd ed. R H Williams (editor). Saunders 1962.
- Soffer L J, Dorfman R I, & J L Gabrielson. The Human Adrenal Gland Lea & Febiger, 1961.

## ADRENAL CORTICAL HYPOFUNCTION (Adrenocortical Insufficiency)

### 1 ACUTE ADRENAL INSUFFICIENCY (Adrenal Crisis)

#### Essentials of Diagnosis

- Onset of weakness, abdominal pain, high fever, confusion, nausea, vomiting and diarrhea with infection or pituitary destruction or cortisone withdrawal.
- Low BP, often sparse axillary and pubic hair and increased skin pigmentation.
- Serum sodium low, serum potassium high, blood and urine corticoids low.
- Eosinophilia, elevated  $\Delta\text{PV}$ .

This condition must be differentiated from other causes of coma and confusion such as diabetic coma, cerebral vascular accident and acute poisoning and from other causes of high fever. Eosinophilia which is usually absent in other emergencies helps in the differentiation. Note: If the diagnosis is suspected, treat with corticoids immediately while awaiting the results of laboratory tests.

#### General Considerations

Acute adrenal insufficiency is a true medical emergency caused by sudden marked deprivation or insufficient supply of adrenocortical hormones. Crisis may occur in the course of chronic insufficiency in a known Addisonian patient out of control or it may be the presenting manifestation of adrenal insufficiency. It may be a temporary exhaustion or may go on to permanent insufficiency. Acute crisis is more commonly seen in diseases of the cortex itself than in disorders of the pituitary gland causing secondary adrenocortical hypofunction.

Adrenal crisis may occur in the following situations: (1) Following stress, e.g. trauma, surgery, infection or prolonged fasting in a patient with latent insufficiency. (2) Following sudden withdrawal of adrenocortical hormone after replacement in a patient with chronic insufficiency or in a patient with normal adrenals but with temporary insufficiency due to suppression. (3) Following bilateral adrenal ectomy or removal of a functioning adrenal tumor which had suppressed the other adrenal. (4) Following sudden destruction of the pituitary gland (pituitary necrosis) or when thyroid or insulin are given to a patient with panhypopituitarism. (5) Following injury to both adrenals by trauma, hemorrhage, thrombosis, infection or rarely metastatic carcinoma. In overwhelming sepsis (principally meningococemia), massive bilateral adrenal hemorrhage may occur (Waterhouse-Friderichsen syndrome).

#### Clinical Findings

**A Symptoms and Signs** The patient complains of headache, lassitude, nausea and vomiting and often diarrhea. Costovertebral angle pain and tenderness (Rogoff's sign) and confusion or coma may be present. Fever may be  $40.5^{\circ}\text{C}$  ( $105^{\circ}\text{F}$ ) or more. The BP is low. Other signs include cyanosis, petechiae (especially with meningococemia), dehydration, abnormal skin pigmentation with sparse axillary hair and lymphadenopathy.

**B Laboratory Findings** A normal or high eosinophil count (200 or above) in the presence of severe stress due to trauma in

fection and other mechanisms is strongly suggestive of adrenal failure. The blood glucose and serum sodium levels are low. Serum potassium and NPN are high. Blood culture may be positive (usually meningococci). Urinary and blood cortisol levels are very low.

C ECG shows decreased voltage

### Complications

Any of the progressive complications of the initiating disease may occur. The complications of treatment or those occurring during the course of treatment are discussed below.

When treatment is instituted, certain complications may be observed. Hyperpyrexia, loss of consciousness, generalized edema with hypertension, and flaccid paralysis due to low potassium has followed excessive use of I.V. fluids and corticoids. Psychotic reactions may occur with cortisone therapy.

### Treatment

The patient must be treated vigorously and observed constantly until well out of danger. Note: It is better to overtreat rather than to undertreat.

#### A Severe Crisis

1 Emergency treatment - Institute appropriate antishock measures (see p. 2) especially I.V. fluids and plasma, vasopressor drugs, and oxygen. Do not give narcotics or sedatives.

Give sulfadiazine or other indicated anti-infective agents as for meningococcal meningitis (see p. 635) and hydrocortisone phosphate or hydrocortisone sodium succinate (Solu-Cortef®), 100 mg I.M. or I.V. stat and repeat 50 mg every 6 hours for the first day. Give the same amount every 8 hours on the second day and then gradually reduce the dosage every 8 hours.

If hydrocortisone hemisuccinate or prednisolone phosphate is not available, give cortisone acetate 10-25 mg I.M. in 4 different sites (to a total of 40-100 mg) following with single injections of cortisone 25-50 mg I.M. every 6 hours and gradually lengthen the intervals of administration to 20 mg every 8 hours.

If parenteral hydrocortisone, prednisolone, or cortisone is not available, or if the

patient is unresponsive, give aqueous adrenocortical extract, 20-50 ml I.V. stat and follow with 100-200 ml in 1 L. of saline-dextrose as an I.V. infusion.

2 Convalescent treatment - When patient is able to take food by mouth, give oral cortisone 12-25 mg every 6 hours and reduce dosage to maintenance levels as needed.

B Moderate Crisis - If the patient's physical condition does not appear to be critical and is not associated with a significant degree of shock, the treatment outlined above may be modified by appropriate reduction in dosage. However, it is generally best to overtreat the patient in moderate crisis during the first 24 hours rather than risk undertreatment.

#### C Complications During Treatment

Excessive use of I.V. fluids and corticosteroids may cause high fever, loss of consciousness, generalized edema with hypertension, flaccid paralysis due to potassium depletion, and psychotic reactions.

1 Overhydration usually due to sodium retention may result in cerebral edema (with unconsciousness or convulsions) or pulmonary edema. Withhold sodium and fluids temporarily and treat for these conditions.

2 Hypokalemia. Flaccid paralysis with low serum potassium usually occurring on the second to fourth days of treatment may be treated with potassium salts.

3 Hyperpyrexia is rare with present treatment methods.

4 For other complications of adrenal steroid therapy (e.g. psychotic reactions), see p. 584.

### Prognosis

Before replacement therapy and antibiotics became available, acute adrenal crisis was often rapidly fatal. Even today if treatment is not early and vigorous, death occurs in several hours. Once the crisis has passed, the patient must be observed carefully to assess the degree of permanent adrenal insufficiency.

Lipsett, M.B., & O.H. Pearson. Pathophysiology and treatment of adrenal crisis. *New England J Med* 254:511-4, 1956.

## 2 CHRONIC ADRENOCORTICAL INSUFFICIENCY (Addison's Disease)

### Essentials of Diagnosis

- Weakness easy fatigability anorexia frequent episodes of nausea vomiting and diarrhea
- Sparse axillary hair increased skin pigmentation of creases pressure areas and ripples
- Hypotension small heart
- Serum sodium and chloride and urinary 17 ketosteroids and 17 hydroxycorticoids are low Serum potassium and NPN are elevated Eosinophilia and lymphocytosis are present

Differentiate from anorexia nervosa sprue syndrome and malignant tumors Weakness must be differentiated from that due to hyperparathyroidism hyperthyroid myopathy and myasthenia gravis skin pigmentation from that of primary skin diseases argyria and hemochromatosis The serum electrolyte abnormalities may resemble those of salt losing nephritis and low sodium states with chronic pulmonary disease

### General Considerations

Addisonism was a rare disease before the advent of adrenal surgery for cancer hypertension and other disorders It is characterized by chronic deficiency of hormones concerned with glycoastasis and with mineral metabolism and causes unexplained and often striking skin pigmentation Electrolyte deficiencies may be the dominant manifestation and may even be associated with excess of adrenal androgens (see adrenogenital syndrome) If chronic adrenal insufficiency is secondary to pituitary failure (atrophy necrosis tumor) lack of glycoastasis is more commonly seen than electrolyte deficiencies and skin pigmentationary changes are not encountered

Tuberculosis accounts today for less than half of cases and in this form the electrolyte deficiencies are more striking Idiopathic atrophy accounts for most of the other cases and in this group hypoglycemia is more striking than the electrolyte changes

Rare causes include metastatic carcinoma (especially of the breast or lung) cocaine oldomycosis of the adrenal gland syphilis gummas scleroderma Amyloid disease and hemochromatosis There may be associated hypoparathyroidism and candidiasis

### Clinical Findings

**A Symptoms and Signs** The symptoms are weakness and fatigability anorexia nausea and vomiting diarrhea nervous and mental irritability and faintness especially after missing meals Pigmentary changes consist of diffuse tanning over nonexposed as well as exposed parts or multiple freckles or accentuation of pigment over pressure points and over the nipples buttocks perineum and recent scars Black freckles may appear on the mucous membranes of tongue Seven to 15% of patients have associated vitiligo

Other findings include hypotension with small heart hyperplasia of lymphoid tissues stiffness of the cartilages of the ear (Thorn's sign) scant to absent axillary and pubic hair (especially in females) absence of sweating severe dental caries and at times costovertebral angle tenderness

**B Laboratory Findings** The WBC shows moderate neutropenia (about 5000/cu mm) lymphocytosis (30-50%) and a total eosinophil count over 300/cu mm Hemoconcentration is present Serum sodium and chloride are low serum potassium and NPN are elevated Urinary 17 ketosteroid and 17 hydroxycorticoid excretion is low The fasting blood glucose level and BMR are low Low blood corticoids (less than 8 mcg/100 ml) are diagnostic

Adrenal calcification on x ray may be found in about 10% of cases

**C Special Tests** (1) The four hour corticotropin test (Thorn test) is confirmatory if total blood eosinophils fail to fall by at least 50% within 4 hours following the administration of 40 units of corticotropin IM (2) The eight hour I V corticotropin test consists of giving 25 units of corticotropin in 1000 ml of physiologic saline by I V infusion in primary Addison's disease the 24 hour urine 17 ketosteroid and 17 hydroxycorticoid values fail to rise in adrenal insufficiency secondary to pituitary insufficiency or in patients who have had suppressive corticoid therapy there is a slow abnormal rise of 17 ketosteroid and 17 hydroxycorticoid levels at times only after several days of stimulation (3) Tolerance tests are dangerous and rarely used Robinson Kepler Power water test Cutler Power Wilder test prolonged fasting glucose and insulin tolerance test

**D ECG Findings** The ECG shows low voltage and prolonged P R and Q-T intervals

**E EEG Findings** Slowing of electric discharges (reversed by cortisone but not by desoxycorticosterone)



### Complications.

Any of the complications of the underlying disease (e.g., tuberculosis) are more likely to occur, and the patient is susceptible to intercurrent infections which may precipitate crisis. Diabetes mellitus and rarely, thyrotoxicosis may be associated.

The dangers of overzealous treatment as well as inadequate replacement must be guarded against. Psychoses, gastric irritation, and low-potassium syndrome may occur with cortisone treatment. Steroid treatment may impair the patient's resistance to tuberculosis, which may spread. Excessive desoxycorticosterone administration is rare today, but formerly led to hypertension, edema, anasarca, muscular weakness, and tendon contractures. Hypercalcemia is particularly apt to occur in children, especially when the adrenocortical level is suddenly reduced.

### Treatment.

#### A. Specific Therapy

1. Cortisone or hydrocortisone are the drugs of choice. Most Addisonian patients are well maintained on 12.5-37.5 mg. of compound E or 10-40 mg. of compound F orally daily in 3-4 divided doses. On this dosage most of the metabolic abnormalities are corrected. Most patients, however, do not obtain sufficient salt-retaining effect from these drugs, and require desoxycorticosterone or fludrocortisone supplementation or extra dietary salt.

2. Fludrocortisone acetate has a potent sodium-retention effect. The dosage is 0.1-0.25 mg. orally daily or every other day.

3. Desoxycorticosterone acetate (DOCA®) controls electrolyte balance and has no other significant metabolic effect. It may be given 1 M. initially, but this is rarely necessary. The usual dose is 1-4 mg. 1 M. daily. When the response is adequate, give buccally, 1 tablet (2 mg.) daily or at most 1 tablet (2 mg.) twice daily. The tablet is placed between cheek and teeth and allowed to dissolve.

Desoxycorticosterone trimethylacetate, 25-75 mg. 1 M. once monthly, may be used instead, desoxycorticosterone trimethylacetate (25 mg.) 1 M. once monthly = about 1 mg. desoxycorticosterone acetate in oil per day.

Caution: Whenever using desoxycorticosterone acetate or fludrocortisone, avoid overdosage. Do not place the patient on a low-potassium diet when giving these drugs, for he may develop potassium deficiency.

4. Sodium chloride in large doses (5-20 Gm. daily) may be used to supplement cortisone therapy instead of desoxycorticosterone acetate or if DOCA or fludrocortisone is not available.

B. General Measures Give a high-carbohydrate, high-protein diet. Frequent small feedings tend to be better tolerated than 3 large ones. Prevent exposure to infection and treat all infections immediately and vigorously. Methyltestosterone, 10-20 mg. daily orally, testosterone propionate in oil, 10-25 mg. 1 M. 3 times weekly, or testosterone cyclopentylpropionate (Depo-Testosterone®) or testosterone enanthate (Delatestyl®), 200-400 mg./month, is often helpful for its protein anabolic effect and for the nonspecific feeling of well-being it induces in the debilitated patient.

C. Treatment of Complications Treat spread of tuberculosis (especially renal tuberculosis) and intercurrent infections with appropriate measures. The treatment of complications due to overdosage or inadequate dosage of corticosteroids consists of adjusting the dosage or in some cases discontinuing therapy for a short time.

#### Criteria of Adequate Therapy & Overdosage.

##### A. Adequate Therapy

1. Return of BP to normal (may require up to 3-4 months)
2. Maintenance of normal fasting blood glucose level.
3. Return of serum electrolytes to normal levels.
4. Weight gain (usually due to fluid).
5. Improvement of appetite and strength.
6. Increase in size of heart to normal.

B. Overdosage Excessive administration of cortisone or desoxycorticosterone acetate must be avoided, especially in patients with cardiac or renal complications.

1. Signs and symptoms of cortisone overdosage are discussed on p. 583.
2. Development of dependent edema, or excessive weight gain.
3. Development of hypertension.
4. Increase of diameter of heart above normal.
5. Development of signs of potassium deficiency (weakness followed by loss of muscle power and finally paralysis), especially if the patient is on a low-potassium diet.

#### Prognosis.

With adequate replacement therapy the life expectancy of patients with Addison's disease is markedly prolonged. Active tuberculosis may respond to specific chemotherapy. Withdrawal of treatment or increased demands due to trauma, surgery, or other types of stress may precipitate crisis with a sudden

fatal outcome. Pregnancy may be followed by marked exacerbation of the disease. Psychotic reactions may interfere with management.

The ultimate prognosis depends largely upon the intelligence of the patient and the availability of medical supervision. A fully active life is now possible for the majority of patients.

Gutman P H. Addison's disease: statistical analysis of five hundred sixty six cases and a study of pathology. Arch Path 10: 742-85 and 895-935, 1930.

Hills G A, Zintel A H & D W Parsons. Observations of human adrenal cortical deficiency with special reference to replacement therapy with cortisone. Am J Med 21: 358-79, 1956.

## ADRENOCORTICAL OVERACTIVITY

Overactivity of the adrenal secretions is caused either by bilateral hyperplasia or by adenoma or more rarely carcinoma of the adrenal. The clinical picture will vary with the type of secretion produced but in general 3 clinical disorders can be differentiated: (1) Cushing's syndrome in which the glucocorticoids predominate; (2) the adrenogenital syndrome in which the adrenal androgens predominate; and (3) aldosteronism with electrolyte changes. The clinical picture is most apt to be mixed in cases of malignant tumor and in bilateral hyperplasia. All syndromes of adrenal overactivity are far more common in females than in males.

### 1. CUSHING'S SYNDROME (Adrenocortical Hyperfunction) & CUSHING'S DISEASE (Pituitary Basophilism)

#### Essentials of Diagnosis

- Buffalo obesity, easy bruisability, psychosis, hirsutism, purple striae and acne associated with impotence or amenorrhea.
- Osteoporosis, hypertension, glycosuria.
- Elevated 17 hydroxycorticoids, low serum potassium and chloride, low total eosinophils and lymphopenia.
- Special x-ray studies may reveal a tumor or hyperplasia of the adrenals.

Differentiate from obesity and postmenopausal osteoporosis in diabetic females. Psychoses, hypertension or glycosuria may dominate the picture and must be differentiated from other causes of these conditions.

#### General Considerations

This disorder is due to an excess of cortisone-like substances elaborated by the adrenal cortex. The adrenal cortex is always involved either by hyperplasia or by adenoma or carcinoma but a basophilic pituitary adenoma may be the primary lesion.

Hyperplasia of both adrenal cortices is the most common form (80%). Adenoma of one adrenal (single adenoma) is the next most common form (15%) and this type often constitutes the clearest form of Cushing's syndrome. The opposite adrenal is atrophic.

Carcinoma of the adrenal (5%) is always unilateral and often metastasizes late. A mixed picture with virilization is often present. The opposite adrenal is atrophic.

Adrenal rest tumors in the ovary rarely cause Cushing's syndrome; they are more commonly associated with virilizing syndromes.

Carcinoma of the anterior pituitary is a most unusual cause of Cushing's disease.

Administration of corticotropin causes adrenal hyperplasia; administration of cortisone causes adrenal atrophy associated with some features of Cushing's syndrome. These effects are reversible when medication is withdrawn.

Rarely, certain malignant tumors (e.g. bronchogenic oat cell carcinoma) have been reported to produce severe Cushing's syndrome with bilateral adrenal hyperplasia.

#### Clinical Findings

**A. Symptoms and Signs.** Cushing's syndrome or disease causes moon face and buffalo hump, obesity with protuberant abdomen and thin extremities, a plethoric appearance, oligomenorrhea or amenorrhea (or impotence in the male), weakness, backache, headache, hypertension, mild acne and superficial skin infections, chloasma-like pigmentation (especially on the face), hirsutism (mostly of the lanugo hair over the face and upper trunk, arms and legs), purple striae (especially around the thighs, breasts and abdomen) and easy bruisability (e.g. hematoma formation following venipuncture). Patients with Cushing's disease or syndrome are less prone than normal people to develop colds or allergic disorders. Mental symptoms may range from increased lability of mood to frank psychosis.

**B. Laboratory Findings** Glucose tolerance is low, often with glycosuria. The patient is resistant to the action of insulin. Urinary 17-hydroxycorticoids and blood corticoids are high (the latter over 20 mcg./100 ml.) Urinary 17-ketosteroids are often low or normal in Cushing's syndrome due to adenoma; normal or high if the disorder is due to hyperplasia; and very high if due to carcinoma. Total eosinophils are low (under 50/cu. mm.), lymphocytes are under 20%, and RBC and WBC are elevated. Serum  $\text{CO}_2$  is high and serum chloride and potassium are low in some cases, especially those associated with malignant tumors.

**C. X-ray Findings** Osteoporosis of the skull, spine, and ribs is common. Nephrolithiasis may be seen. I.V. urograms or retroperitoneal pneumograms may demonstrate a tumor of the adrenal or bilateral enlargement. X-ray of the sella is usually not helpful since basophilic adenomas are very small.

**D. ECG** may show characteristic signs of hypertension and hypokalemia

#### E. Special Tests

1. **ACTH stimulation test** - The administration of ACTH causes marked hypersecretion of urinary 17-ketosteroids and 17-hydroxycorticoids in Cushing's disease or syndrome due to hyperplasia or adenoma but does not stimulate secretion in cases due to carcinoma.

2. **Cortisone suppression test** - Administration of fludrocortisone or its derivatives in large doses (e.g., dexamethasone, 2 mg every 6 hours for 2-3 days) suppresses the activity of hyperplastic adrenals but has no effect on adrenal hyperactivity due to adenoma or carcinoma

#### Differential Diagnosis.

The most difficult problem is differentiating true Cushing's syndrome from obesity associated with diabetes mellitus, especially if there is hirsutism and amenorrhea. The distribution of the fat, the virtual absence of virilization, and the laboratory studies often help, but are not infallible. Cushing's syndrome must be differentiated from the adrenogenital syndrome (see below), since the latter may be amenable to medical treatment unless it is caused by tumor. The 2 diseases may coexist. An elderly woman with osteoporosis, diabetes, and mild hirsutism may present a difficult problem in differentiation.

In rare cases the outstanding manifestation of Cushing's disease or syndrome may be only diabetes or only hypertension or only

psychosis. Adrenal disease must be ruled out in patients with these disorders, especially in insulin-resistant diabetes mellitus, since treatment may be curative.

#### Complications.

The patient may suffer from any of the complications of hypertension, including congestive failure, cerebrovascular accidents, and coronary attacks, or of diabetes. Susceptibility to infections, especially of the skin and urinary tract, is increased. Compression fractures of the osteoporotic spine may cause marked disability. Most serious, perhaps, are the psychotic complications not infrequently observed in this disease. After adrenalectomy, pituitary enlargement (due to chromophobe adenomas) and deepening skin pigmentation have been observed

#### Treatment.

##### A. Specific Measures

1. **Surgical removal of the tumor or total or subtotal resection of both adrenals** (in the case of diffuse bilateral hyperplasia) is the present treatment of choice. Adequate preoperative medication and care are of utmost importance. The patient should receive all general measures listed below, plus adequate hormonal supplementation.

If bilateral adrenalectomy is contemplated, give high doses of the cortisones, e.g., cortisone acetate, 100-300 mg. I.M., or, preferably, 100-300 mg. of Solu-Cortef® in divided doses I.M. or I.V., on the day of surgery, continue the I.M. dosage after surgery. After surgery, gradually decrease the dose and maintain as for Addison's disease. Because of the danger of precipitating heart failure, care must be taken to avoid excessive fluids and sodium

In cases of unilateral tumor, the patient is prepared as for total adrenalectomy. After surgery, corticotropin as well as cortisone may be given to stimulate the atrophic gland. Treatment with cortisone may have to be continued for weeks since the gland may be slow to recover function.

2. **X-ray therapy to the pituitary** (either alone, or following unilateral adrenalectomy) may be of value in selected cases of hyperplasia.

**B. General Measures** A high-protein diet should be given, although dietary attempts to correct the negative nitrogen balance are never successful. Testosterone or one of the newer anabolic agents may be of value in reversing the negative nitrogen balance. Potassi-

um chloride administration may replace losses before and after surgery

Insulin is usually of little or no value in controlling the glycosuria and hyperglycemia, and is usually unnecessary as the diabetes is quite mild

### Prognosis

This is a chronic disease which is subject to cyclic exacerbations (especially with pregnancy) and spontaneous remissions; it is a serious and often fatal disease unless discovered and treated early. A rather rapid course suggests a malignant tumor, but these may be dormant for years.

The best prognosis for eventual recovery is for patients in whom a benign adenoma has been removed and who have survived the post-adrenalectomy state of adrenal insufficiency. A small number of patients with bilateral hyperplasia may respond to pituitary irradiation alone or combined with subtotal adrenalectomy.

Complete adrenalectomy necessitates chronic replacement therapy, which is feasible today.

Malignant tumors are usually fatal, even after such drastic attempts at treatment as hypophysectomy.

Cope O & J W Raker. Cushing's disease: the surgical experience in the care of 46 cases. *New England J Med* 253:119-27 and 165-73 1955

Pitlor C M, Knowlton A I & C Ragan. The natural history of Cushing's syndrome. *Am J Med* 13:597-614 1952

## 2. THE ADRENOGENITAL SYNDROME PREPUBERAL

### Essentials of Diagnosis

- Abnormal urogenital development noted at birth or precocious development early in life
- Enlarged clitoris or phallus, hirsutism, short stature, excessive muscular development, acne, seborrhea
- 17-ketosteroids elevated, FSH absent to low, pregnanetriol elevated

Differentiate from Cushing's syndrome, constitutional precocity and precocity secondary to hypothalamic

or pineal lesions or interstitial tumors of the testes. In the female the adrenogenital syndrome must also be distinguished from true hermaphroditism.

### General Considerations

This disorder is produced by androgenic excess due either to adrenal hyperplasia (often familial) or adrenal tumors, and manifests its virilizing effects by interfering with the normal sexual development of the fetus, infant or child. The congenital form of the adrenogenital syndrome is due to hyperplasia, the childhood form occurring after normal intrauterine development may be due either to tumor or to hyperplasia. Congenital adrenocortical hyperplasia is rare, often familial, much more common in females and often associated with an addisonian-like state in male infants. Rarely congenital virilization is caused by testosterone or progesterone administration to the pregnant mother.

### Clinical Findings

#### A. Symptoms and Signs

1. Congenital adrenocortical hyperplasia. In females pseudohermaphroditism, enlargement of the clitoris, urogenital sinus formation and later hirsutism are found. In males phallic enlargement (macrogenitosomia praecox), precocious virilization and (in infants) an addisonian-like state which may be confused with pyloric stenosis, characterized by nausea and vomiting, dehydration and electrolyte deficiencies.

2. Adrenogenital syndrome in children. Somatic growth is accelerated, bone age is accelerated with early epiphyseal closure and short stature. Other findings include excessive muscular development (infant Hercules), precocious virilization and in some cases acne and seborrhea. With tumors the clinical features of Cushing's disease may be present. Hypertension may occur.

B. Laboratory Findings. Bone age is advanced on x-ray examination, 17-ketosteroids are elevated for the age. I V urograms or retroperitoneal oxygen studies may demonstrate adrenal pathology. FSH is absent or very low. ACTH stimulation tests and cortisone suppression tests help distinguish normal, hyperplastic, and neoplastic adrenals. Urinary pregnanediol and pregnanetriol excretion is elevated in congenital adrenal hyperplasia and in carcinomas.

**Differential Diagnosis.**

A. In Either Sex: Distinguish from Cushing's syndrome:

	Adrenogenital Syndrome	Cushing's Syndrome
Hirsutism	+++	+
Virilism	+++	0
Growth rate	++	--
Muscles	+++	---
17-Ketosteroids	+++	+
17-Hydroxy-corticoids	N or decr.	+++
Pregnenediol	++	0

B. In Males Differentiate from true isosexual precocity, either constitutional or due to hypothalamic or pineal lesions. In this situation the FSH test is positive and the 17-ketosteroids normal or only slightly elevated the testes are larger than the testes of the adrenogenital boy, and spermatogenesis may occur. The other important condition causing pseudoisexual precocity is unilateral or bilateral interstitial tumor of the testis. These are usually palpable within the scrotum. 17-Ketosteroid excretion is not as high in interstitial tumor as in adrenal tumor.

C. In Females The most important differentiation is from genetic intersexuality (true hermaphrodite with testes, ovotestes or ovaries). 17-Ketosteroid excretion is normal in intersex, and the chromosomal count on a buccal or vaginal smear helps to establish the diagnosis. Premature appearance of hair may cause confusion, but other stigmas of virilization are not present. Since arrhenoblastomas of the ovary do not occur before puberty, they should not cause confusion.

**Treatment.**

Treatment is discussed with the treatment of Adrenogenital Syndrome and Virilizing Diseases of Adult Females on p. 470.

**Prognosis.**

Males with congenital adrenal hyperplasia, even when treated intensively, often die in infancy of severe fluid and electrolyte loss. Some tumors are malignant and often fatal, but early removal will cause regression of virilization. The use of cortisone in bilateral hyperplasia has been most effective in suppressing adrenal virilization and restoring a normal state with breast development, menses etc., in girls and spermatogenesis in males. The ultimate prognosis for patients

who receive cortisone is not yet known, but in some cases remissions have been sustained for several years even though cortisone is discontinued. Normal pregnancy has occurred after long-term cortisone therapy.

Eberlein, W.R., & A.M. Bongiovanni: Pathophysiology of congenital adrenal hyperplasia. Symposium on hereditary metabolic diseases. Metabolism 9:325-40, 1960.

### 3. THE ADRENOGENITAL SYNDROME & VIRILIZING DISEASES OF ADULT FEMALES

**Essentials of Diagnosis**

- Menstrual disorders and hirsutism.
- Regression or reversal of primary and secondary sex characteristics with balding, hoarse voice, acne and enlargement of the clitoris.
- Occasionally a palpable pelvic tumor.
- 17-Ketosteroids elevated in adrenal disorders, variable in others.

Differentiate from racial, familial, and idiopathic hirsutism, which are not associated with disturbances of other sex characteristics.

**General Considerations.**

The diagnosis of virilizing disorders in adult females is more difficult since other sources of abnormal androgens exist, principally the ovaries. There is no interference with formation of the female genital tract or secondary sex characteristics, but rather a regression or sex reversal of varying degree. Although the diagnosis is readily apparent in a complete state of the virilizing syndrome (e.g., the adult form of the congenital adrenogenital syndrome), the milder forms, presenting primarily with defeminization or merely excessive hirsutism, may be caused by equally serious adrenal and ovarian disorders such as tumors. A sudden change in amount of hair (other than at puberty, pregnancy, or menopause) is of greater importance than hirsutism which has been present throughout life.

Besides adrenal hyperplasia and tumors, adult female virilization may be caused by the following disorders: (1) Ovarian disorders: Arrhenoblastoma, Stein-Leventhal syndrome (large, pale ovaries, most common), theca luteinization (thecosis ovarii), hilar cell tu-

mor or hyperplasia adrenal cell rests dysgerminoma (rare) (2) Hypothalamic-pituitary disorders Acromegaly (eosinophilic adenoma) hyperostosis frontalis (Stewart Morgagni-Morel syndrome) (3) Placental causes Pregnancy chorio epithelioma (4) Miscellaneous causes True hermaphroditism thymic tumors drugs (e.g. testosterone)

### Clinical Findings

**A Symptoms and Signs** Symptoms include scant menstrual periods or amenorrhea acne and roughening of the skin odorous perspiration and hoarseness or deepening of voice Hirsutism is present over the face body and extremities with thinning or balding of head hair Musculature is increased and feminine contours are lost The breasts and genitalia are atrophied the clitoris and

Adam's apple enlarged A tumor may rarely be palpable on pelvic examination (arrhenoblastoma polycystic ovaries)

**B Laboratory Findings** Urinary 17 ketosteroid determination is the most important single test in the diagnosis of adrenogenital syndrome It helps differentiate constitutional hirsutism from adrenal disorders in which the 17 ketosteroids are significantly elevated However in arrhenoblastoma or Stein Leventhal syndrome 17 ketosteroids may be moderately elevated The ACTH stimulation test and the cortisone suppression test may distinguish between adrenal tumors adrenal hyperplasia and ovarian lesions

True assay of androgens (e.g., testosterone) in the blood and urine has recently become possible but the tests are not yet available for general use

**C X ray Findings** I.V. urograms or retroperitoneal pneumograms may reveal an adrenal tumor Gynecography may show large ovaries

### Differential Diagnosis

Since hirsutism may be the only sign of adrenal tumor all of the disorders characterized by excessive hair have to be considered in the differential diagnosis From the practical standpoint however the diagnosis commonly depends upon whether one is dealing simply with racial familial or idiosyncratic hirsutism where an unusual end-organ sensitivity to endogenous male hormone exists or whether excessive amounts of male hormone are being produced In general if not only hirsutism but also enlargement of the clitoris and deepening of the voice are present (or loss of head hair) and if the onset is

rapid one can assume that a tumor of the adrenal or ovary is present In these circumstances exploratory operation is mandatory in spite of equivocal laboratory and physical findings Although virilization is not the rule with Cushing's syndrome a mixed picture is at times seen in malignant adrenal tumors and more rarely in hyperplasia

### Complications

Aside from the known high incidence of malignancy in tumors causing virilization the interference with femininity and consequent sterility may be irreversible Diabetes and obesity may be complicating features At times mental disorders accompany states of defeminization

### Treatment

When tumor is present surgical removal is the treatment of choice In some cases of adrenal hyperplasia especially in infancy there may be associated manifestations of hypoadrenocorticism (e.g. excessive salt and water loss and failure to maintain a fasting blood sugar) This condition is apparently due to a congenital absence of hydroxylating enzymes of the adrenals The androgenic compounds formed have no cortisone activity and are unable to suppress endogenous ACTH hence the continued adrenal stimulation and large glands Treatment with corticoids has proved valuable in reducing the activity of the glands (apparently by suppressing endogenous ACTH) and in supplying exogenously needed corticoids In adults the drug of choice appears to be prednisone or prednisolone 5-25 mg daily orally in divided doses use the smallest dose which keeps the 17 ketosteroid and pregnanetriol levels within the normal range

The response of congenital adrenal hyperplasia to long term corticoid steroid therapy is gratifying with lessening of virilization and hirsutism and eventually normal cyclic menstruation Plastic repair (removal of the clitoris and repair of a urogenital sinus) is required Cortisone therapy of milder forms of virilization (e.g. simple hirsutism) is less successful

### Prognosis

The outlook is favorable if a malignant tumor is removed early since metastasis often occurs late Wedge resection of polycystic ovaries may restore fertility Cortisone therapy may be of help in hyperplastic lesions

The ultimate fate of the virilized woman depends not only upon the underlying cause

(i.e., tumor or hyperplasia), but more particularly upon the age at onset of the virilizing influence and its duration. If virilization is of long standing, restoration of normal femininity or loss of hirsutism is unlikely even though the causative lesion is successfully removed.

**Note** Most cases of excessive hirsutism in females are not due to endocrine disease but to hereditary or racial factors and should not and cannot be treated with systemic medications or surgery.

Benson, R.C., Kolb, F.O., & H.F. Traut  
Hirsutism, defeminization, and virilization, the endocrine basis for diagnosis and treatment. *Obst. & Gynec.* 5:307-19, 1955.

## PRIMARY ALDOSTERONISM

### Essentials of Diagnosis.

- Hypertension, polyuria, polydipsia, muscular weakness, tetany
- Hypokalemia, hypernatremia, alkalosis, renal damage
- Elevated urinary aldosterone level
- Tumors too small to be visualized by x-ray.

Differentiate from all types of hypertension, potassium-losing and salt-losing nephritis, nephrogenic diabetes insipidus, and tetany.

### General Considerations.

Primary aldosteronism is a relatively rare disorder caused by aldosterone excess. It is more common in females, and is most often caused by small adrenocortical adenomas (although it is at times found with adrenocortical hyperplasia and very rarely with adrenocortical carcinoma or normal-sized adrenals). Edema is rarely seen in primary aldosteronism, but secondary aldosteronism is often found in edematous states such as cardiac failure and hepatic cirrhosis. Since sodium restriction stimulates aldosterone production, low-sodium diets or diuretic agents must be discontinued before the diagnosis can be confirmed with chemical tests.

### Clinical Findings.

**A. Symptoms and Signs** Hypertension (usually benign), muscular weakness (at times with paralysis simulating periodic paralysis), paresthesia with frank tetanic manifestations, headache, polyuria (especially nocturnal), and

polydipsia are the outstanding complaints. Edema is rarely present

**B. Laboratory Findings** Low serum potassium, hypernatremia, and alkalosis are pathognomonic of primary aldosteronism. Various degrees of renal damage are manifested by proteinuria, alkaline urine, nephrocalcinosis, and low urine specific gravity unresponsive to vasopressin. If spironolactone (Aldactone<sup>®</sup>, 200 mg., or Aldactone A<sup>®</sup>, 50 mg., q.i.d. for 5-8 days) restores serum potassium to normal, suspect hyperaldosteronism. Urinary aldosterone levels are markedly elevated, but this test is not generally available

**C. ECG Findings** ECG changes are due to prolonged hypertension and hypokalemia.

**D. X-ray Findings** Cardiac hypertrophy due to hypertension is the only x-ray finding. The tumors are too small to be visualized.

### Differential Diagnosis.

This important reversible cause of hypertension must be considered in the differential diagnosis in any patient who shows muscular weakness and tetanic manifestations, and in the differential diagnosis of periodic paralysis, potassium- and sodium-losing nephritis, nephrogenic diabetes insipidus, and hypercalcemia and hypokalemia (be certain the patient has not been receiving diuretic agents). Unilateral renal vascular disease produces high aldosterone levels with severe hypertension

### Complications.

All of the complications of severe hypertension are encountered in primary aldosteronism. Progressive renal damage is less reversible than hypertension. The incidence of pyelonephritis and nephrocalcinosis is high.

### Treatment.

The only treatment for primary aldosteronism is surgical removal of adenomas or subtotal resection of hyperplastic glands

Secondary aldosteronism can be effectively treated with the chemical aldosterone antagonist spironolactone (Aldactone<sup>®</sup>)

### Prognosis.

The hypertension is reversible in about two-thirds of cases, but persists or returns in spite of surgery in the remainder. The renal disease is partially reversible, but once pyelonephritis is established it may continue along its natural course.

Prognosis is much improved by early diagnosis.

Conn J W Evolution of primary aldosteronism as a highly specific entity J A M A 172 1650 3 1960

## DISEASES OF THE ADRENAL MEDULLA

### PHEOCHROMOCYTOMA

#### Essentials of Diagnosis

- Spells or attacks of headache, visual blurring, severe sweats, vasomotor changes in a young adult
- Hypertension, often paroxysmal (spells) but frequently sustained
- Postural tachycardia and hypotension, cardiac enlargement
- Elevated BMR with normal PBI, glycosuria, negative cold pressor test, positive provocative (histamine) and blocking agent tests (phenolamine)
- Elevated urinary catecholamines or their metabolites

Differentiate from other causes of hypertension (renal, essential, coarctation). The hypermetabolic symptoms must be distinguished from those caused by thyrotoxicosis and the glycosuria from that due to diabetes mellitus. Differentiate also from psychoneurosis in a young person.

#### General Measures

A not uncommon disease characterized by paroxysmal or sustained hypertension due to a tumor of pheochromocytoma tissue, most commonly located in either or both adrenals (90%) or anywhere along the sympathetic nervous chain and rarely in such aberrant locations as the thorax, bladder or brain. About 10% of patients have multiple tumors and these have a familial tendency. A small percentage become malignant and may show functioning metastases. Pheochromocytoma tumors are associated with neurofibromatosis in about 5% of cases. The tumors, which are more commonly located on the right side, may vary in size and are rarely large enough to be palpable. They contain varying proportions of epinephrine and norepinephrine, with the latter usually predominating (50-90%). Norepinephrine-producing tumors are more likely to cause sustained hypertension; the paroxysmal variety is more common with epinephrine. Pregnancy or trauma is frequently the precipitating event in this disease, which is most common in women between the ages of 20 and 40.

#### Clinical Findings

**A Symptoms and Signs** Pheochromocytoma is manifested by attacks of severe headache, palpitation or tachycardia, profuse sweating, vasomotor changes (including pallor or flushing of the face or extremities), precordial or abdominal pain, nausea and vomiting, visual disturbances (including blurring or blindness), aphasia and loss of consciousness (rarely), increasing nervousness and irritability, increased appetite, dyspnea, angina and loss of weight. Physical findings include hypertension, either in attacks or sustained with cardiac enlargement, postural tachycardia (change of more than 20 beats/minute) and postural hypotension, mild elevation of basal body temperature, abdominal or flank tumor (in about 5%) and, rarely, transient swelling of the thyroid. Retinal hemorrhage or papilledema occurs occasionally.

**B Laboratory Findings** The cold pressor response is negative (BP fall or a rise of less than 20/15). BMR is elevated. PBI is normal and glycosuria or hyperglycemia (or both) is present. An attack of hypertension may in rare cases be produced by massage of either flank.

#### C Special Tests

1 **Provocative test** (for use during the normotensive phase) The histamine test is positive if administration of histamine causes release of medullary hormone and consequent rise in BP. **Caution:** Phenolamine (Regitine®) should be on hand in case BP rise is excessive.

2 **Blocking agent test** (for use during the hypertensive phase) Administration of phenolamine (Regitine®) or piperoxan (Benodaine®) blocks medullary hormone and causes a fall of BP.

3 **Assay of urinary catecholamines** on a 24-hour urine specimen - and a simpler test for 3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid, VMA) - are now generally available. The levels of these urinary constituents will be elevated in all cases of sustained and most cases of paroxysmal hypertension due to pheochromocytoma.

4 The most reliable test for pheochromocytoma associated with paroxysmal hypertension is direct assay of epinephrine and nor epinephrine in the blood and urine during or following an attack. Proper collection of specimens is essential.

#### Differential Diagnosis

Pheochromocytoma should always be suspected in any patient with labile hypertension, especially if some of the other features such as



elevated BMR or glycosuria are present in a young person. Because of such symptoms as tachycardia, tremor, palpitation, and high BMR, pheochromocytoma is often confused with thyrotoxicosis. About 10% are mistakenly treated as diabetes mellitus because of the glycosuria. Pheochromocytoma may also be misdiagnosed as essential hypertension, glomerulonephritis or other renal lesions, toxemia of pregnancy, eclampsia, and psychoneurosis. It rarely masquerades as gastrointestinal hemorrhage and abdominal disorders of an emergency nature. Serotonin tumors may present a similar clinical picture but are quite rare. Conversely, the presence of an abdominal tumor such as aortic aneurysm or renal cyst in a patient with a falsely positive phentolamine test for pheochromocytoma has led to an erroneous diagnosis. Although false-positive tests are not uncommon with pharmacologic agents and may lead to unnecessary explorations, the occasional false-negative test may permit a potentially curable fatal disease to go unrecognized. The availability of urinary catecholamine determination has made the diagnosis much more accurate.

#### Complications.

All of the complications of severe hypertension may be encountered. Hypertensive crises with sudden blindness or cerebrovascular accidents are not uncommon. These may be precipitated by sudden movement, by manipulation during or after pregnancy, by emotional stress or trauma, or during surgical removal of the tumor.

After removal of the tumor, a state of severe hypotension and shock (resistant to epinephrine and norepinephrine) may ensue with precipitation of renal failure or myocardial infarction. These complications can be avoided by judicious preoperative and operative use of blocking agents such as phentolamine.

Occasionally a patient dies as a result of the complications of diagnostic tests or during surgery.

#### Treatment.

Surgical removal of the tumor or tumors is the treatment of choice. This may require exploration of the entire sympathetic chain as well as both adrenals. Administration of phentolamine before and during surgery and postoperative maintenance with norepinephrine and cortisone have made this type of surgery a great deal safer in recent years.

Since there may be multiple tumors, it is essential to recheck urinary catecholamine postoperatively.

Long-term medical treatment with phentolamine is not successful.

#### Prognosis.

The prognosis depends entirely upon how early the diagnosis is made. If the tumor is successfully removed before irreparable damage to the cardiovascular system has occurred, a complete cure is usually achieved. Complete cure (or improvement) may follow removal of a tumor which has been present for many years. Rarely, hypertension persists or returns in spite of successful surgery. Only a small percentage of tumors are malignant.

Before the advent of blocking agents the surgical mortality was as high as 30%, but this is rapidly being reduced.

If after removal of a tumor a satisfactory fall of BP does not occur, always consider the presence of another tumor.

It has been estimated that in the United States alone about 800 deaths a year are due to unrecognized pheochromocytoma.

Roth, G. M., & others. Pharmacologic and chemical tests as an aid in the diagnosis of pheochromocytoma. *Circulation* 21:769-78, 1960.

## DISEASES OF THE PANCREATIC ISLET CELLS

### DIABETES MELLITUS

#### Essentials of Diagnosis

- Glucose found in urine on routine testing
- Polyuria, polydipsia, polyphagia, weight loss, somnolence, pruritus, paresthesias
- Retinal microaneurysms and vitreous hemorrhages, skin infections, premature atherosclerosis with angina and claudication, peripheral neuritis
- Hyperglycemia, decreased glucose tolerance, hypercholesterolemia

Diabetic glycosuria must be differentiated from other causes of reducing substances in the urine which give a false-positive urine glucose test, renal glycosuria, and alimentary hyperglycemia and glycosuria. Distinguish also from stress glycosuria and insulin-resistant diabetes, seen in pituitary

lesions and adrenal lesions, and glycosuria seen in thyrotoxicosis and pheochromocytoma. Any patient with a strong family history of diabetes must be suspected of having the disease.

### General Considerations.

Diabetes mellitus is probably the most important of all endocrine diseases. Over 4% of females and 2% of males in the United States are or will eventually become diabetic. The disease affects all age groups, and the incidence in children under fifteen is 4/10,000. The exact cause of diabetes mellitus is not known, but the major metabolic defect may be corrected by the administration of insulin.

Most of the metabolic abnormalities in diabetes can be traced to the inability of the organism to metabolize glucose properly, which in turn places an undue stress on protein and fat catabolism for the availability of energy. Insulin is concerned not only with the utilization of glucose, but also with its storage as glycogen in the liver, if insulin is lacking, the capacity of the organism to store glycogen is impaired. Insulin is also important in lipogenesis.

There is good evidence that there are 2 different types of diabetes: (1) true deficiency of pancreatic islets, and (2) imbalance of the other regulatory hormones or production of insulin antibodies, which tends to increase the blood glucose.

Prolonged hyperglycemia in diabetes with underutilization of glucose will lead to increased protein and fat catabolism. Prolonged hyperglycemia and hyperlipemia may lead to premature vascular degeneration, with coronary and peripheral atherosclerosis, a peculiar type of renal disease, intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease) and retinal degeneration with microaneurysms and eventual retinitis proliferans. Additional pathologic changes noted are neuropathy, severe nephrosclerosis or chronic pyelonephritis and, more rarely, papillary renal necrosis. The incidence of infections is markedly enhanced.

Early detection and treatment has in part forestalled some but not all of the serious and fatal complications of diabetes. By and large the life expectancy of the adult diabetic who is well controlled and does not undergo repeated episodes of coma or insulin shock is about the same as that of a normal person of the same age. The outlook for the juvenile diabetic is not so favorable.

There is a well-known hereditary predisposition to diabetes and the greater inci-

dence in the obese is demonstrated by insurance statistics. The maternal and fetal mortality rate is much higher in diabetic women than in normal women. Trauma, infections, and emotional stress often precipitate the disease in susceptible persons.

### Clinical Findings.

**A Symptoms.** Polyuria and excessive thirst may go unnoticed for years. Nocturia and enuresis may occur in juvenile diabetics. Increased appetite and loss of weight are common in children but rare in adults. Pruritis (especially of the vulva and anal mucous membranes) is usually present. Asthenia, somnolence, paresthesias, and impotence may occur.

### B Signs

1 Ocular manifestations - Refractive changes, premature cataracts, retinopathy with microaneurysms, vitreous and retinal hemorrhage, optic neuritis.

2 Skin manifestations - Mycotic infections (candidiasis, perleche), carotenemia (xanthosis), xanthomatous tumors (rare), boils or carbuncles (common).

3 Cardiovascular-renal manifestations - Atherosclerosis manifested by premature coronary atherosclerosis, non-healing ischemic leg ulcer with gangrene, edema, heart failure.

4 Neurologic manifestations - Peripheral neuritis, areflexia, loss of vibration sense, neurogenic bladder, nocturnal diarrhea.

**C Laboratory Findings.** Although none of the tests described below are pathognomonic of diabetes, the diagnosis rests on laboratory determinations because the clinical features of the disease are so variable. The principal laboratory signs of diabetes are glycosuria, hyperglycemia, decreased glucose tolerance, and elevated serum cholesterol.

1 Glycosuria - The presence of reducing substances identified as glucose in the urine is excellent presumptive evidence of diabetes. Reducing substances in the urine may be identified with any of the following tests: (1) Benedict's qualitative test. Add 8 drops of urine to 5 ml. of Benedict's qualitative solution and bring to a boil. Responses vary from blue (negative) to brick red (4+). (2) Clinistix<sup>®</sup> tablets placed in a test tube with 5 drops of urine and 10 drops of water show reducing substance by means of color reactions as observed with Benedict's test. The tablets must be fresh. (3) Clinistix<sup>®</sup> and Tes-Tape<sup>®</sup> are impregnated papers which identify glucose in the urine by means of specific color reactions.

2 **Hyperglycemia** - Determine the fasting blood glucose and postprandial glucose levels (before and 2 hours after a meal containing 50-100 Gm. of carbohydrate). An initial fasting blood glucose of 200 mg /100 ml or more is almost conclusive evidence of diabetes, a fasting blood glucose above 140 mg /100 ml with a high postprandial blood glucose is very strong evidence of diabetes.

3 **Glucose tolerance tests** - Since a normal fasting blood glucose level does not rule out diabetes, and since the postprandial blood glucose is occasionally elevated in other disorders (e.g., liver disease), glucose tolerance tests are performed. This is also true in borderline cases, i.e., when the fasting blood glucose levels are between 100 and 140 mg /100 ml (Note: It is not necessary and it may be harmful to perform a glucose tolerance test in a patient whose initial fasting blood glucose level is over 200 mg /100 ml). If this test is performed, be certain the patient has had a high-carbohydrate intake for 48-72 hours before the test, since carbohydrate restriction decreases tolerance.

(1) The standard glucose tolerance test is performed as follows: Take an initial blood sample from a fasting patient, have him empty his bladder, and give 100 Gm. of glucose in 300 ml. of water orally. Obtain samples of blood and urine for glucose determination one-half hour, one hour, 2 hours, and 3 hours later. In normal people the fasting and two-hour blood samples will contain less than 120 mg /100 ml of glucose and the half-hour specimen will contain less than 180 mg /100 ml (Folin-Wu). The one-hour and two-hour blood specimens in conjunction with the other specimens are of value in interpreting the severity of diabetes or detecting other causes of hyperglycemia in the event that tolerance is shown to be decreased. The urine samples are taken so that the threshold for glucose can be correlated with the blood findings to fortify the diagnosis. In addition to the standard three-hour glucose tolerance test there are several modifications, e.g., a one-hour, two-dose test, and I V tests.

(2) The insulin tolerance test is of greatest value in differentiating insulin-sensitive diabetes from "insulin-resistant" forms such as may occur in acromegaly and Cushing's disease. It is performed as follows: Give 0.1 unit of crystalline zinc insulin per Kg. ideal body weight I V. Determine the blood glucose levels immediately and at 20, 30, 45, 90, and 120 minutes. Normal sensitivity to insulin will cause the blood glucose level to fall to half its initial value, or below 50 mg /100 ml. In 20-30 minutes, with return to normal levels in 90-120 minutes.

(3) The **Orinase<sup>®</sup>** tolerance test to determine "insulin reserve" is of value in assessing insulin production when the diagnosis of diabetes is questionable, e.g., in the prediabetic state. Give 1 Gm. of sodium tolbutamide (Orinase<sup>®</sup>) I V in 20 ml. of physiologic saline solution. Failure of the normal fasting blood glucose level to fall by 30-50% within 30 minutes indicates limited insulin production. This is seen in the prediabetic state as well as in the diabetic.

(4) **Cortisone test** - Decreased glucose tolerance following a short course of cortisone therapy is considered by some authors to be evidence of the prediabetic state.

4 **Serum cholesterol** is often increased in diabetes.

**C X-ray Findings** - A plain film of the abdomen may show evidence of calcification of the pelvic blood vessels. This is an especially unfavorable sign in a young patient.

### Differential Diagnosis

Ten to 15% of patients whose routine urinalyses show glycosuria do not have diabetes mellitus. These positive reactions are due to urine sugars other than glucose, urine constituents which are not sugars but which give positive reactions and benign nondiabetic glycosuria (the most common problem in diagnosis). Fructosuria, pentosuria, and galactosuria are usually asymptomatic, but can be identified with special tests. Salicylates, alkaptonic amino acids, and other substances in the urine may also give false-positive reactions to Benedict's test, but the use of Tes-Tape<sup>®</sup>, which is specific for glucose, will eliminate the source of confusion. Benign nondiabetic glycosuria may occur in renal glycosuria, i.e., overflow of glucose at normal blood glucose levels as a result of a tubular defect, often familial and associated with other tubular defects such as the De Toni-Fanconi syndrome. It may occur during pregnancy. Alimentary hyperglycemia and glycosuria may occur in states of rapid absorption or poor storage capacity, e.g., dumping syndrome, starvation, or liver disease. They can be ruled out by observation of the glucose tolerance curve.

Transient emotional or stress glycosuria is attributable to epinephrine or to adrenal stress hormones. True diabetes mellitus develops eventually in about 10% of these patients, or the two types may coexist when the patient is first seen.

Also to be differentiated is the insulin-resistant diabetes seen in pituitary and adrenal

lesions and the glycosuria which is present in thyrotoxicosis and pheochromocytoma

### Complications

#### A Acute Complications

1 Diabetic ketosis acidosis and coma (see p 550)

2 Insulin reactions (actually a complication of therapy) usually occur when there is a sudden change in insulin requirement. The principal symptoms are weakness, hunger, irritability, tremor and coma or convulsions (or both) all of which are promptly relieved by giving glucose. In addition and especially with protamine zinc insulin, confusion or even psychotic reactions are not uncommon. If the diagnosis of insulin reaction is in doubt, a therapeutic trial of glucose is indicated. Diabetics should carry proper identification.

3 Insulin allergy - Itches or painful lumps at the site of injection

B Chronic Complications. Certain complications notably infections (e.g. around the toenails) and degenerative vascular diseases, occur more frequently among people with diabetes than in the general population. The following disorders may appear in long-standing diabetes:

1 Premature arteriosclerosis with leg claudication, trophic ulcer, angina

2 Neuropathy varying from paresthesias to actual muscular atrophy. Neuropathy is also the cause of nocturnal diarrhea and bladder atony.

3 Ocular disorders ranging from premature cataracts, microaneurysms and vitreous hemorrhage to retinitis proliferans and blindness.

4 Inter-capillary glomerulosclerosis (Kimmelstiel-Wilson disease) with associated hypertension, proteinuria and edema.

5 Pyelonephritis (common) and papillary necrosis (rare).

6 Chronic pyogenic infections of the skin.

7 Xanthomas (only in long-standing uncontrolled cases).

8 An unusual skin lesion, necrobiosis lipoidica diabetorum, may appear in the diabetic patient, as well as fat atrophy and hypertrophy at the sites of insulin injections.

9 The incidence of tuberculosis in the diabetic is higher than in the general population.

10 Insulin resistance - For unexplained reasons the insulin required may suddenly (at times temporarily) increase tremendously.

### Treatment \*

The treatment of diabetes mellitus requires a thorough understanding of the action

of insulin and the various types of insulin available. Dietary concepts, the influence of exercise, the complications of the disease and the complications which may arise as a result of its treatment and the use of the oral hypoglycemic agents.

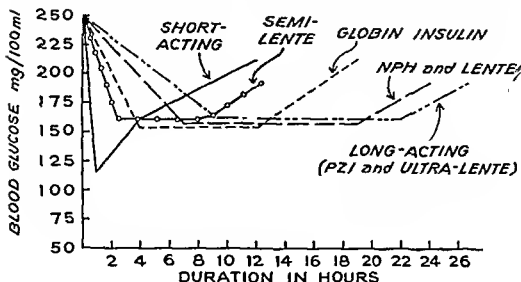
A Insulin. Insulin is given to enhance carbohydrate utilization. This is measured clinically by noting the lowering of the blood glucose or the lessening or disappearance of glycosuria.

Three principal types of insulin are available: short-acting, long-acting and intermediate-acting. Short-acting insulin (crystalline zinc insulin) is useful mainly in controlling postprandial blood sugar elevations in the treatment of diabetic coma and when the insulin requirement is changing rapidly (e.g. as postoperatively). Long-acting insulins are useful for controlling the milder hyperglycemia which is present during the remainder of the time between meals. The 2 forms available are protamine zinc insulin (PZI) and ultra-lente insulin, which is similar in effect to PZI (although its effect may be prolonged to 48-72 hours). Intermediate-acting insulin is available in several forms: (1) Isophane insulin (NPH), a stable mixture with properties much like a 2:1 mixture of crystalline zinc and PZI insulin, has tended to replace PZI in the management of most diabetic patients. It may also be 'tailored' to fit the patient by the addition of appropriate amounts of regular insulin. (2) Lente insulin, a mixture of 30% semi-lente and 70% ultra-lente, is made by the action of zinc on insulin under special conditions (protamine-free and phosphate-free). Its action is almost identical with that of NPH insulin. (3) Globin zinc insulin is similar in action to a 2:1 insulin mixture except that its duration of effect is not so prolonged. It is useful in many diabetic patients but it cannot be mixed with short-acting insulin. (4) Semi-lente insulin has the shortest action of all the intermediate insulins.

Insulin Mixtures\*. Intermediate insulin may be prepared by mixing a short-acting or intermediate (commercial) and a long acting insulin (add last) in the same syringe. This gives a balance between the immediate and the prolonged effects by modifying the mixtures. One can tailor the insulin requirements to individual needs. The mixtures usually employed are 2:1 and 3:1 (crystalline zinc PZI) or 2:1 and 3:1 (NPH PZI). Crystalline insulin must always be drawn into the syringe before

\*See also Steps in the Management of the Diabetic Patient p 555

Extent &amp; Duration of Action of Various Types of Insulin (in a Fasting Diabetic)



PZI (because of the protamine excess in PZI) and the same concentration/ml of crystalline insulin and PZI must be used. The general effect of crystalline zinc PZI mixtures is as follows: 1 l gives essentially the same effect as PZI alone and there is little point to this mixture; 2 l gives an intermediate daytime-nighttime effect; and 3 l gives a greater daytime effect.

Tailored insulin mixtures are used as follows: (1) If glycosuria occurs in all urines, increase total insulin mixtures; (2) If glycosuria occurs in urines voided before lunch and dinner (daytime glycosuria), increase the proportion of crystalline zinc insulin in the mixture; (3) If glycosuria occurs in urines voided before bedtime and before breakfast (nighttime glycosuria), increase the proportion of PZI mixture.

Commercial insulin preparations come in various strengths (units/ml) usually in 10 ml vials. Most of them are prepared in U40 and U80 forms. Crystalline zinc insulin is also available as U100 and U500.

**Administration of Insulin.** Because the large number of insulin preparations available may cause confusion regarding dosage, it is recommended that the patient be placed on one type of insulin so that he can become familiar with it. Prescribe an insulin of such strength that the volume/injection is kept at 0.25-0.5 ml. About 80% of patients are able to use U40 insulins.

Syringes are calibrated in units (U) rather than ml. If syringes with 2 calibrations (U20-

U40 or U40-U80) are used, it is important that the patient should understand which scale he is using. It is preferable, however, to use a syringe with one calibration only. Special syringes are available for blind diabetic patients.

Insulin is usually administered subcutaneously. The site of injection is generally the anterior thigh, but insulin may also be given in the lateral thigh, in the arms or anterior abdomen or in unusual circumstances subcutaneously in other parts of the body. It is important that the sites be rotated so that the same site is not injected more often than once every 2-3 weeks. Crystalline zinc insulin may be administered I.V. to patients who have been taking insulin without allergic reactions. **Note:** Do not give PZI, NPH, or lente insulin I.V.

**B Diet.** The nutritional needs of the diabetic patient are not significantly different from those of normal individuals. The principal question to be settled is the quantity and type of carbohydrate to be allowed in the diet. The chart on p. 52 gives detailed instructions for diabetic diets. **Note:** Whenever possible, diabetic diets should be made up in terms of household measurements rather than weight; the greater accuracy gained by weighing foods is not clinically necessary.

The following factors must be taken into consideration in estimating the diet:

1. **Caloric needs.** The caloric needs of the diabetic are estimated as for a nondiabetic person, and the same variables must be con-

sidered. In general the diabetic patient should be kept at normal or slightly subnormal weight levels and should not be permitted to become obese.

2 Protein - Adequate protein must be given. High protein diets are desirable because the available glucose (58%) from protein is released more slowly for utilization than ingested carbohydrate. At least 1 Gm of protein/Kg should be given although 1.5-2 Gm/kg are preferable.

3 Carbohydrate - Carbohydrate should not be given in concentrated form. Preference should be given to 3 and 7% vegetables and 10-15% fruits; these take longer to digest and to absorb and a less variable blood glucose level is obtained. The question of adequate versus restricted carbohydrate in the diet is still unsettled. In general the aim of dietary management is to keep the patient as close to physiologic normal as possible. This implies that his carbohydrate intake should be at about normal levels and insulin administered as necessary to control hyperglycemia and glycosuria. In general therefore 2-3 Gm of carbohydrate/Kg is recommended at the start of treatment. If the patient's tolerance increases with treatment gradually increase carbohydrate intake to 4 Gm/Kg. This is only a general rule however and in some mild cases it may be advisable to restrict carbohydrates so that the use of insulin can be avoided. Both for physiologic and for psychologic reasons the carbohydrate level should in no case be below 100 Gm/day.

4 Fat - After the carbohydrate and protein components of the diet have been determined fat is given to make up the remaining caloric requirements. The type of fat to be administered should be considered in view of the high incidence of atherosclerosis in patients with diabetes and the fact that serum cholesterol levels are also often high. It may be important to reduce serum cholesterol levels. Giving fats high in unsaturated fatty acids is the most effective way to achieve this objective (see p 51). Some authors prefer to give diets very low in fat to patients with diabetic retinopathy.

5 Vitamins - Patients with diabetes tend to develop vitamin deficiencies especially of the B complex. The reasons are not always clear. If deficiencies occur treat as required (see p 588).

6 Frequency of feeding - Diabetics should be given small frequent feedings rather than large meals. By frequent feedings the use of high-protein intake and less concentrated carbohydrate foods one can maintain a lower and more even blood sugar level with

less glycosuria. An excellent plan is to divide the feedings into 6 meals: 3 regular meals and 3 small feedings (e.g., milk) at midmorning, midafternoon, and bedtime.

C Oral Hypoglycemic Agents - These agents are of 2 types: (1) the sulfonylurea group of drugs (useful primarily in the older diabetic with a mild form of the disease) and (2) the biguanide group of drugs (which are effective in reducing blood sugar in almost all diabetics).

In substituting one of the oral agents for insulin in a patient who has been taking insulin it is well to remember that insulin can be discontinued abruptly only in those patients who do not develop ketosis without insulin. In patients who do develop ketosis it is advisable to decrease the insulin dosage slowly, adding the oral agents at first in small doses and gradually increasing the dosage and observing the patient closely for side reactions.

1 Sulfonylurea drugs - Tolbutamide (Orinase<sup>®</sup>) and chlorpropamide (Diabinese<sup>®</sup>) are sulfonamide derivatives although neither has antibacterial properties. Their apparent mode of action is to stimulate the production of insulin by the beta cells of a pancreas which would not otherwise produce adequate amounts. They do not potentiate the action of insulin and are of no value unless the pancreas is capable of secreting insulin. Therefore these drugs are of limited use (and should rarely be tried) in severe diabetes (e.g., juvenile onset) or in those diabetic patients who tend to develop ketosis easily. Their only area of usefulness is in the older patient with a mild degree of diabetes which cannot be controlled by diet alone (relatively mild adult maturity onset, nonketotic types). Tolbutamide is supplied in tablets of 0.5 Gm. Give an initial dose of 3 Gm daily in divided doses and decrease rapidly to the minimal effective dose. The average maintenance dose is 0.5-1.5 Gm daily. Toxic reactions are rare; skin rashes and gastrointestinal distress occur only occasionally. Chlorpropamide is supplied in tablets of 0.5 Gm. This drug has a greater duration of action than tolbutamide (up to 3-5 days). Always start patients on 0.5 Gm daily. The average maintenance dosage is 0.25-0.5 Gm; rarely 1 Gm daily may be required. Toxic reactions are probably more frequent than with tolbutamide and jaundice has been reported.

2 Biguanides - Phenformin (DBF<sup>®</sup>) supplied in tablets of 25 mg exerts a hypoglycemic action either in the absence or presence of insulin. Its mode of action is not known but phenformin appears to inhibit gluconeogenesis.

genesis from protein and possibly increases anaerobic glycolysis. It is not known whether these reactions are harmful. The drug seems to be of use in "juvenile" diabetics to lower insulin requirements or help stabilize brittle diabetics. The chief side reactions are gastrointestinal disturbances with higher effective doses. The recent introduction of long acting capsules of 25 and 50 mg has lessened this tendency and improved control. The usual starting dose is 25 mg b i d, the usual maintenance dose is 50-100 mg daily in divided doses. Note: Ketonemia and acidosis may be aggravated by phenformin, and additional insulin must be given if this occurs.

#### D Other Factors Influencing Diabetes

1 Exercise - Exercise enhances the oxidation of sugar hence it diminishes the need for insulin. Therefore, exercise in moderation is beneficial. However patients taking insulin should be cautioned against strenuous exercise without fortifying themselves previously with extra carbohydrate (It is not uncommon to have a hypoglycemic reaction after a set of tennis). When regulating a patient, have him perform approximately the same amount of exercise as will be required during his normal activities. This is true also of hospital-regulated diabetics.

2 Complicating factors - Many factors adversely affect the course of diabetes by altering the absorption of glucose, by interfering with carbohydrate oxidation or by causing excessive carbohydrate formation. The most important of these factors are infections especially pyogenic infections with fever and toxemia. Any infection is serious in a diabetic patient because it completely upsets the equilibrium established by therapy, increases the need for insulin and is one of the most common precipitating causes of ketosis and acidosis. Infections should therefore be avoided whenever possible, when they occur, they must be treated promptly and vigorously. During severe infections it is generally advisable to discontinue PZI and NPH insulin and to begin therapy in divided doses 3-6 times daily with crystalline zinc insulin as needed to cover postprandial glycosuria.

3 General factors - Patients with diabetes should live as nearly normal hygienic lives as possible. They should be assured of adequate rest, should be able to eat at home if possible, and should engage in an occupation requiring at least moderate exercise but must avoid strenuous occupations of greatest importance. They should have a good general knowledge of diabetes.

#### Steps in the Management of the Diabetic Patient.

There are many adequate methods for managing diabetes. The following is a plan used by the authors which is felt to be both practical and physiologically sound.

##### A Diagnostic Examination

1 Complete history and physical examination for diagnosis and to rule out the presence of coexisting or complicating disease.

2 Urinalysis for qualitative glucose on a morning fasting urine specimen and on specimens collected 2-3 hours after each meal. If glucose is present check for acetone and diacetic acid.

3 Blood glucose examination - Fasting and 2-hour postprandial levels are determined or, if necessary, a glucose tolerance test performed. In elderly patients or in the presence of renal disease it is advisable to perform a glucose tolerance test with simultaneous urine glucose to determine the approximate renal threshold. If this is very high (over 160-180 mg/100 ml) it may be necessary to use blood glucose levels rather than the glycosuria as a check on adequacy of therapy.

##### B Calculation and Arrangement of Diet (See p 52 for examples of diabetic diets)

1 Determine the caloric needs of the patient. These are the same as for the nondiabetic (see p 45).

2 Calculate the protein, carbohydrate, and fat content of the diet as outlined in Chapter 3.

3 Divide the diet into 6 feedings as follows: (1) Three medium-sized meals spaced as far apart as possible (i.e. an early breakfast and a late dinner) this will spread the absorption of glucose over a longer period of the day. (2) Three small feedings to be taken between meals and at bedtime. Milk and low-carbohydrate fruits are preferred.

##### C Determination of the Insulin Requirements

1 Determine amount of glycosuria. Have the patient eat his diabetic diet for one day preferably without change in activity. For the next 24 hours he is to collect and label fractional urines as follows: (Patient voids just before breakfast and discards this specimen.) Urine No. 1, all urine voided from breakfast to just before lunch. This is pooled and a few drops taken for qualitative sugar. The re-

mainder is saved Urine No 2 all urine from lunch to just before dinner Pool and save as above Urine No 3 all urine from dinner to just before retiring Pool and save as above Urine No 4 all urine from retiring to just before breakfast Pool and save as above A few drops of each urine fraction are analyzed qualitatively for glucose and the remainder pooled for the daily total quantitative glucose determination

2 Calculate the approximate insulin requirements from quantitative urine sugar determinations Since roughly one unit of insulin will cover 2 Gm of glucose the insulin needs in the uncomplicated diabetic can be calculated as follows

Gm of Glucose in 24 Hour Urine Specimen	Approximate Number of Units of Insulin Needed per 24 Hours
2	

The 24-hour insulin requirement is generally given as NPH or as a mixture in a single dose one-half hour before breakfast The usual mixtures are 2 i or 3 i (crystalline zinc PZI) or NPH crystalline mixture In severe or complicated diabetes because the patient needs insulin immediately this method of determining the requirement cannot be used (See p 557) Also in certain elderly patients or those with renal disease who have a high renal threshold for glucose this method will be without value These patients must be controlled by the determination of the blood glucose levels while fasting and one hour after meals In these cases begin with small doses of long-acting insulin (5-10 units/day) and increase as indicated by tests

3 Adjustment of insulin dosage and mixture - The patient continues to collect his urine fractions as outlined above and the dosage and composition of the insulin mixture is determined each morning after completing the qualitative glucose analysis for the previous day Quantitative glucose determinations are usually not necessary after the first day The amount and time of glycosuria on the preceding day determine the readjustment to be made The glycosuria at any time should be kept at a minimum i e., no greater than green reduction (or +) with enzymatic test paper methods in any specimen In general especially with longer-acting insulins changes should not be made frequently simply because marked insulin reactions occasionally occur

(1) If all specimens are green no adjustment of dosage or composition of insulin is necessary

(2) If glycosuria (greater than green reduction) occurs after breakfast or after the

noon meal the proportion of crystalline zinc insulin in the mixture is increased

(3) If glycosuria occurs in the afternoon after the evening meal or before breakfast the proportion of protamine zinc insulin in the mixture is increased or it may be preferable to give a second smaller dose of NPH insulin at bedtime

(4) If glycosuria occurs in all specimens both crystalline zinc and protamine zinc insulins must be given in higher dosages

(5) The amount of insulin which should be added will vary with each patient A very rough guide is as follows Yellow reduction (or ++ ) add up to 5 units orange reduction (or +++ ) add 5-10 units brick-red reduction (or ++++ ) add 10-15 units

(6) If there is no glycosuria (specimen remains blue) the patient should be questioned for evidence of hypoglycemia and each urine voided should be examined Adjustment of dosage must be made in accordance with the findings

4 Readjustment of the size of feedings - If variations of the insulin dosage and composition do not maintain the glycosuria at a minimum for a given period the dietary intake for the preceding meal should be decreased and the intake for other meals increased a similar amount

D Follow up of Patient After the patient has been adequately controlled he should be seen at regular intervals

1 Hypoglycemic reactions - Carefully question the patient about the occurrence of any hypoglycemic reactions If these occur reduce the insulin dosage according to the time of day the reactions take place

2 Examine the urine - If all urine is entirely free of glucose the patient is controlled (if the renal threshold is normal) However if all urines are blue early in therapy be careful of hypoglycemic reactions since the patient's tolerance will improve under therapy There is no contraindication to having some green reductions If there is marked glycosuria in any urine, the insulin dosage is adjusted accordingly

3 Weigh the patient to be sure that the weight is increasing decreasing or remaining stationary as desired If not alter the diet accordingly

4 Draw blood for fasting blood glucose test to determine whether fasting hyperglycemia is being adequately controlled (This need not be done on every visit In fact it can be done quite infrequently once the patient's control is stabilized)



### Complications of Insulin Therapy

**A Hypoglycemia** Hypoglycemia is the most common complication of insulin therapy. It usually occurs when the patient fails to eat or engages in too strenuous exercise. It is manifested by weakness, hunger, sweating, irritability, faintness, and tremors and convulsions, all of which are relieved promptly by the administration of glucose. If a diabetic patient is seen while unconscious and if a diagnosis of coma or insulin reaction is impossible or in doubt, give 50% glucose 1 V. This will definitely overcome the insulin reaction and will not generally harm the patient in diabetic acidosis.

Because of the danger of insulin reaction the diabetic patient should carry several lumps of sugar or glucose lozenges at all times. If he feels the onset of a reaction, he should take some sugar.

Every diabetic should carry a card with the following information:

#### I Am a Diabetic and Take Insulin

If I am behaving peculiarly, give me sugar or hard candy or orange juice slowly. If I am unconscious, call an ambulance immediately, take me to a physician or a hospital, and notify my physician. I am not intoxicated.

My Name \_\_\_\_\_

Address \_\_\_\_\_

Telephone \_\_\_\_\_

Physician's Name \_\_\_\_\_

Physician's Address \_\_\_\_\_

Telephone \_\_\_\_\_

**Treatment** If the patient is conscious and able to swallow (mild hypoglycemia), sugar, glucose, or orange juice may be given. If the patient is unconscious (moderate to severe hypoglycemia), one of 4 methods may be used (Do not attempt to feed glucose to an unconscious patient.)

(1) **I V glucose** (treatment of choice) Give 20-50 ml of 50% glucose 1 V slowly. As soon as consciousness returns, oral feedings may begin.

(2) **Glucagon**. One mg I V will restore the blood glucose to normal if the hepatic glycogen reserve is adequate. This drug does not

cause the autonomic side-effects which occur with epinephrine. The solution is not stable.

(3) **Epinephrine**. If the patient is well nourished and especially if he has been using short acting insulin and the liver is not depleted of glycogen, epinephrine 0.5-1 ml of 1:1000 solution subcut. may cause return of consciousness so that food may be taken by mouth.

(4) **Rectal feeding**. If the patient is unconscious and 1 V glucose is not available (and if epinephrine is either not available or not feasible or successful), glucose by rectum may be life saving. Add 2 Tbsp of syrup or honey to a pint of warm water and give slowly by rectum.

When patients taking protamine zinc insulin develop reactions, they should be carefully watched for the possibility of relapse. High-protein foods such as milk should be given in addition to carbohydrate.

**B Allergic Reactions**. Fortunately, allergic reactions to insulin are very rare and most are localized. Patients who develop reactions are usually sensitive to pork pancreas from which about 60% of commercial insulin is made (the other 40% is from beef pancreas). These patients should be given pure beef insulin preparation (Special Insulin) which is supplied in 10 ml vials containing 40 units/ml. If this does not prevent reactions, desensitization measures should be tried.

**C Lipatrophy**. This rare complication consists of atrophy of subcutaneous fat at the sites of insulin injection. It may be due to improper rotation of injection sites, but some cases occur in spite of careful therapy. These patients should use U80 or U100 insulin, rotate injection sites, and inject only on body areas which are clothed at all times.

### Prognosis

Although diabetes is still an unpredictable disease, since the advent of insulin and antibiotics, the life expectancy of the adult diabetic is about the same as that of other people. The ultimate outcome depends in part upon the duration of the illness (juvenile diabetics fare worse than adults) and the adequacy of treatment. The greater the number of episodes of coma and insulin reactions, the worse seems to be the generalized vascular degeneration, especially of the peripheral arteries and the coronary arteries. Other factors than strict control seem to be responsible for the progression of retinal and renal changes. Strict attention to hygiene, periodic x-rays of the chest, and vigorous treatment of minor infections often will forestall major complications.

The juvenile diabetic often shows marked lability of control this together with emotional factors makes him more liable to complications

Pregnancy (see p 560) and the menopause seem to increase the severity of diabetes and diabetes is associated with a greater incidence of toxemia edema and prolonged gestation with large babies and hydramnios Strict supervision during pregnancy and early termination of pregnancy have reduced these hazards

Special attention is also required when the diabetic patient has to undergo surgery (see p 561)

The insulin requirement once established may vary from time to time Sudden unexplained and temporary periods of marked insulin resistance requiring extremely large amounts of insulin may make management difficult Likewise increased sensitivity to insulin with periods of hypoglycemia especially in the sleeping hours may aggravate the vascular degeneration and may lead to permanent mental changes

It is always wise to make sure that the patient presenting himself as a diabetic actually has diabetes and that he does not have a potentially curable disease such as acromegaly pheochromocytoma thyrotoxicosis or Cushing's disease in a subtle form If detected early before permanent damage to the pancreas has taken place the diabetic state in these disorders will improve with cure of the primary disease Likewise should a sudden change in insulin sensitivity take place one must consider associated lesions of the adrenal or pituitary

In general it can be stated that the ultimate prognosis of the diabetic is directly related to his intelligence and motivation and to his personal understanding of his disease and its potential complications Some complications however notably the retinal and renal complications progress relentlessly in spite of the best treatment which raises some doubts as to the ultimate benefit of even rigid diabetic control The results of pituitary surgery or irradiation in hopeless cases with vascular complications e.g. blindness are controversial

The use of the oral antidiabetic agents in the potential diabetic or in the prediabetic state is now under investigation and may materially alter the ultimate prognosis of diabetes mellitus and its complications

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## DIABETIC KETOSIS, ACIDOSIS & COMA

### Essentials of Diagnosis

- Nausea vomiting excessive thirst fruity breath odor hyperpnea fever and increasing somnolence
- History of diabetes with poor control
- Soft eyeballs warm dry skin rapid thready pulse low BP
- Hyperglycemia and glycosuria positive urine and plasma acetone low serum CO<sub>2</sub> high NPN lipemia and cholesterolemia

Differentiate from other causes of coma e.g. cerebrovascular accident and drug toxicity and from insulin excess and false positive acetone test due to drugs Nausea and vomiting must be differentiated from that due to primary gastrointestinal disease

### General Considerations

The transition from ketosis to coma may be subtle and progressive and may escape detection Certain factors especially infection vomiting and diarrhea may suddenly precipitate coma This is more prone to occur in juvenile diabetics

### Clinical Findings

**A Symptoms and Signs** Although the symptoms of ketosis are few there may be mild nausea excessive thirst or malaise which may progress to those of acidosis with vomiting drowsiness hyperpnea and fever Abdominal pains and diarrhea at times with a rigid abdomen may be present The typical fruity odor of acetone may be detected on the breath On physical examination the skin and mucosa are dry the eyeballs soft and the BP low with a rapid and thready pulse

This may progress to loss of consciousness or coma

**B Laboratory Findings** 4+ acetone and sugar in the urine positive urinary diacetic acid, elevated blood glucose, low serum  $\text{CO}_2$ , serum potassium usually elevated, serum sodium and chloride low Plasma acetone is positive The NPN is elevated Lipemia is present

### Differential Diagnosis

The diagnosis is at times difficult without a history or laboratory data In most cases in a known diabetic it is possible to decide whether loss of consciousness is due to coma or excess insulin on clinical grounds alone While awaiting laboratory data, it is always safe to administer I V glucose immediately if no response occurs, coma is not due to insulin excess An abdominal emergency or cerebrovascular accident may cause confusion, and its coexistence with coma cannot be ruled out readily Once coma and acidosis are controlled, the situation usually becomes clarified Rarely, toxic reactions to drugs (e.g. salicylates) may be confusing, especially if a positive reaction for urine glucose or ketone is present Lack of response to treatment is the important clue in these cases

### Treatment.

**A Diabetic Ketosis Without Acidosis** The patient should be hospitalized for regulation if ketosis is severe Treat any infection which may aggravate the disordered metabolism Arrange the diet to consist of 3 equal feedings plus interval feedings between each meal and in the evening If ketosis is severe, use only short-acting insulins Give insulin to cover each meal as necessary until the urine is free of ketone bodies Then reduce the insulin dosage slowly as tolerance to carbohydrate improves If ketosis is not severe, treat and regulate as for uncomplicated diabetes

When ketonuria has cleared, the patient is managed as for uncomplicated diabetes according to the severity of his disease

**B Diabetic Acidosis and Coma** (For emergency management, see below) The principles of therapy are the same whether the patient is precomatose or in coma It is imperative that a patient with acidosis be hospitalized and treated as a medical emergency Each case must be individualized Insulin in large amounts is necessary to bring about a return to normal metabolism Use short-acting insulin Note: Never treat patients in coma with PZI, NPII, or lente insulin The

first dose of insulin should be 100-200 units, one-half should be given I V and the other half subcut Insulin may also be added to I V fluids Because of the mode of action of insulin, there is no need to repeat sooner than in 1-2 hours The dose may then be repeated subcut or I V, giving 50-75 units every 1-2 hours as needed until the ketonuria begins to disappear If shock is present, the insulin should be given I V, because of the unreliable absorption during shock of material given subcut

In diabetic acidosis one is treating the ketosis and acidosis and not the hyperglycemia and glycosuria Although the patient with acidosis may have a high blood glucose level, the total available carbohydrate stores may actually be very low Therefore, since it is necessary to have an adequate glucose supply upon which insulin can act in overcoming acidosis these patients should be given glucose when the blood glucose level has begun to fall rapidly It has been shown that ketosis can be reduced by giving large amounts of glucose to diabetic patients who are deprived of insulin The sooner the normal metabolic pathways are reestablished, the sooner excess fat oxidation ceases and ketonemia is overcome In addition, it is possible to precipitate a hypoglycemic reaction in a patient with low glucose reserves before the ketosis is brought under control

Fluids must be given to replace those lost by diuresis and vomiting These are usually best given I V

Adequate sodium chloride is very important This replaces fixed base in the extracellular fluid and so helps in overcoming the acidosis As a result of ketosis the loss of sodium chloride from the body may be as high as 30 Gm (50% of average total body sodium) in 24-48 hours In the mild case, sodium chloride must be replaced, sodium chloride solution with glucose is usually adequate fluid therapy

As the ketone bodies are excreted or oxidized  $\text{CO}_2$  is returned which replaces the disappearing ketones and the  $\text{CO}_2$  combining power returns to normal However, in patients with severe uncomplicated metabolic acidosis, it may be advisable to administer more rapidly available  $\text{HCO}_3^-$  and fixed base This may be given I V as sodium bicarbonate or sixth-molar sodium lactate

During the period of acidosis, potassium is lost from the cells As sodium is administered (as sodium chloride, sodium bicarbonate, or sodium lactate) and glucose is metabolized and stored, the potassium which has entered the extracellular fluid migrates rapidly intracellularly or is washed out with the fluid

through the kidneys. When this occurs there may be a temporary and dangerous extracellular potassium deficiency with weakness, respiratory distress and at times cardiac arrest. Solutions containing potassium must be given to correct this and generally when I V glucose becomes indicated potassium may be added to the infusion mixture. It must be used with extreme caution in the absence of adequate urinary output. The level may roughly be checked with the ECG (see p. 34).

1. Emergency measures. The following outline of therapy may be employed in the average patient in diabetic coma; however, each case must be individualized and therapy modified as necessary according to the needs of the patient.

(1) Hospitalize the patient and keep him warm but avoid excessive warmth. Do not give barbiturates or narcotics.

(2) If he is in shock, treat with I V plasma and other shock measures, especially vasopressors (see p. 4).

(3) Draw blood for  $\text{CO}_2$  combining power and blood glucose and for serum sodium, potassium and chloride if these tests can be performed.

(4) Give insulin at once. Through the same needle used for drawing blood, give 50-100 units of crystalline insulin I V stat, as well as a like amount subcut. Repeat insulin giving 50-75 units subcut every 1-2 hours until there is a rapid diminution in blood or urine glucose.

(5) Catheterize the patient. An indwelling catheter may be left in place, allow this to drain continuously. Examine urine specimens every hour for ketone bodies and sugar.

(6) Fluids, electrolytes and glucose. Begin an I V infusion of physiologic saline solution. A clysis of saline, sixth-molar sodium lactate or other indicated solutions may be started at the same time. As soon as the urine glucose has changed to olive or green reduction, change I V fluids to 5% glucose in saline to which is added 0.5-1 unit of insulin/Gm of glucose (25-50 units insulin/L) and 20 mEq potassium and possibly phosphate. The urine should contain glucose at all times to avoid hypoglycemic reactions.

As soon as reports come from the laboratory, if  $\text{CO}_2$  combining power is below 5 mEq/L (10 Vol %), administer sodium lactate or sodium bicarbonate I V immediately. (To administer sodium bicarbonate I V, merely dissolve chemically pure sodium bicarbonate in 200-300 ml. cool distilled water and administer.) Note: Do not heat or sterilize the solution.

Gastric lavage may be performed with or without the introduction of 200 ml. of physio-

logic saline or 5% sodium bicarbonate.

As long as the patient is unconscious, administer 5% glucose in saline or other salt solution as indicated (about 60 drops/minute).

As soon as the patient is conscious and able to swallow, give fruit juice (200 ml. of orange juice with 1 Tbsp. of honey syrup or glucose) every 3-4 hours until ketonuria has disappeared. Stop I V glucose and fluids.

## 2. Follow-up Care -

(1) Potassium deficiency. After 4-8 hours of administration of I V fluids, watch the patient carefully for potassium deficiency (e.g., weakness, respiratory distress) and check the ECG (see p. 34). Give solutions containing potassium as indicated. It may be advisable to begin administration of potassium as soon as the coma treatment is begun, but this is still not settled. When the patient is able to swallow, give supplementary potassium salts by mouth (the safest route).

(2) Oral feedings and fluids. If ketonuria is disappearing or is rapidly improving (usually in 24-48 hours) and the patient is conscious, a small frequent feeding of liquid and semiliquid foods containing 50-75 Gm glucose and protein (e.g., as milk) every 3-4 hours day and night and cover with 25-35 units of crystalline zinc insulin every 4 hours, force fluids by mouth and examine the urine for sugar and ketone bodies every 3-4 hours.

(3) Regular diet. After 24-48 hours if the patient shows steady improvement, place on a regular diabetic diet and begin regulation as outlined on p. 555.

## Prognosis

Prognosis depends largely upon the duration of coma, the age of the patient, the severity of unconsciousness and the principal cause of coma (e.g., infection). In spite of apparently good treatment, the mortality remains around 3%.

Moorhouse, J. A., & R. M. Hark. Fructose

and diabetes. *Am. J. Med.* 23:46-58, 1957.

Smith, K., & H. E. Martin. Response of dia-

betic coma to various insulin dosages.

*Diabetes* 3:287-95, 1954.

Trevel, R. W., & E. C. Leighton. The problem of increasing azotemia during management of diabetic acidosis. *Am. J. Med.* 24:368-75, 1958.

## THE DIABETIC PATIENT & PREGNANCY

The management of the pregnant diabetic is little different from that of any other dia-

betic Early in pregnancy there is often a lowering of the renal threshold for glucose and considerable lability of the blood glucose level. During the latter 3 months a marked decrease in glucose tolerance often necessitates increased insulin dosage. This is not universal, however, and many patients go through pregnancy without significant changes in tolerance.

Before the onset of labor and delivery it is advisable to change to short-acting insulins to avoid possible reaction due to lack of food.

In view of work suggesting "sex-hormonal imbalances" in pregnant diabetics, therapy with estrogens or progesterone (or both) has been said to be of value in reducing the fetal mortality rate. However, carefully controlled studies, using modern diabetic treatment methods, show as good or better results without resorting to this expensive and troublesome procedure.

Since many women with diabetes go beyond the anticipated delivery date and because the infants are unusually large, it has been suggested that pregnancy be terminated at about 36 weeks. The preferred method appears to be cesarean section.

#### Care of the Infant

Infants of diabetic mothers should be treated as if they were premature. Keep the infant in an incubator and administer oxygen for the first several days. Observe the newly born infant carefully for the first 72 hours for hypoglycemic reactions which may occur, supposedly as a result of islet cell hyperplasia. This is more apt to occur in infants born to poorly controlled diabetics.

**Medical Council Conference on Diabetes and Pregnancy.** The use of hormones in the management of pregnancy in diabetes. *Lancet* 2:833-6, 1955.

White, P., Gillespie, L. & L. Sexton. Use of female sex hormone therapy in pregnant diabetic patients. *Am J Obst & Gynec* 71:57-69, 1956.

### THE DIABETIC PATIENT & SURGERY

Surgery in the diabetic patient is little more hazardous than the same procedure performed on a nondiabetic patient. However, certain problems are peculiar to the diabetic patient, and these naturally vary with the severity of the disease and the urgency of the operation. A patient who is controlled on oral antidiabetic agents will usually require additional insulin because of the tendency to acidosis.

#### Emergency Surgery

**A For Nontraumatic Conditions.** Diabetics who require emergency surgery for nontraumatic disorders are usually in a state of ketosis with or without acidosis and require immediate treatment of their diabetes. They should be treated as patients with acidosis or coma (the latter if a general anesthesia is to be used). The general program should be as follows:

- 1 Draw blood for  $\text{CO}_2$  combining power and blood glucose, also for serum sodium, potassium and chloride if possible.

- 2 Begin a slow I V infusion of 5% glucose in physiologic saline (not over 70 drops/minute) and continue the infusion throughout the surgical procedure. One unit of insulin/2 Gm. of glucose may be added to the infusion (25 units for each L. of 5% glucose).

- 3 Give 50 units of short-acting insulin I V if ketosis is present.

- 4 Continue therapy postoperatively as for diabetic coma until oral feeding can be given and ketosis and hyperglycemia are controlled.

**B For Traumatic Disorders Requiring Surgery.** Although increased carbohydrate tolerance may develop rapidly as a result of trauma, the principal danger in a treated diabetic who is injured is the possibility of having a severe hypoglycemic reaction because he fails to eat. Therefore if the patient is conscious, give sweetened orange juice or candy by mouth if surgery is necessary, give 5% glucose I V in water or saline slowly. One may add 1 unit of insulin/2-3 Gm. of glucose to the infusion; however, the need is not for insulin so much as for glucose to avoid hypoglycemia. After surgery, treat according to the severity of the disease.

#### Elective Surgery

**A Initial Hospital Measures.** The patient should enter the hospital several days before surgery. Discontinue long-acting insulin. The diabetes should be brought under optimal control with crystalline zinc insulin. Ketosis should be absent.

#### B During and After Surgery

- 1 No food or insulin should be administered on the morning of surgery.

- 2 Management during surgery -

- (1) If the patient's diabetes is mild and has been properly controlled, if he does not tend to develop ketosis, and if the surgery is not too extensive, he may be operated on without I V glucose or insulin.

- (2) If the patient's diabetes is moderate or severe or if extensive surgery must be performed, begin an infusion of 5% glucose in saline or water to which has been added one unit of crystalline insulin/2 Gm. of glucose. Con-

Differential Diagnosis of Hypoglycemic States\*

Type of Hypoglycemia	Fasting Blood Sugar		Glucose Tolerance Curve After Standard Dietary Preparation	Liver Function	Clinical Course, Progression and Time of Attacks	Response to I. V. Ornase <sup>†</sup> Test
	Standard Diet	ClO Restriction or 24-hour Fast				
Functional hyperinsulinism	Normal	Normal†	Normal fasting blood glucose, sharp fall to hypoglycemic levels between second and fourth hours	Normal	Not progressive in severity, more frequent under emotional or physical tension, relief by vacations, etc., no prebreakfast attacks, attacks 2-4 hours after meals, no effect of skipped or late breakfast	After temporary hypoglycemia, blood glucose levels return to normal in 1-2 hours.
Organic hyperinsulinism	Subnormal usually below 50 mg./100 ml	Subnormal always below 40 mg./100 ml, usually below 30 mg./100 ml	Subnormal fasting blood glucose, low level curve, sharp fall to very low levels between second and fifth hours	Normal	Progressive in frequency and severity, prebreakfast attacks frequent from 2 a m to 8 a m, attacks 2-4 hours after meals, attacks precipitated by skipped or late meals, or exercise	Prolonged hypoglycemia
Heptogenic hypoglycemia	Subnormal often below 50 mg./100 ml	Subnormal always below 40 mg./100 ml, often below 30 mg./100 ml	Subnormal fasting blood glucose, hyperglycemic plateau curve with glycosuria, gradual fall to hypoglycemic levels in 4-7 hours	Severely disturbed	Progressive in frequency and severity, prebreakfast the time of most frequent occurrence, 2 a m to 8 a m, daytime attacks rare unless precipitated by skipped meal, sometimes evidence of hepatic disease	Prolonged hypoglycemia.

\*Modified and reproduced, with permission, from J. W. Conn and H. S. Seltzer, Spontaneous Hypoglycemia, *Am. J. Med.* 19:463, 1955.

†During 3 days of severe carbohydrate restriction most normal people show fasting blood glucose levels of 50-60 mg./100 ml. (Somogyi).

tinue the infusion throughout the operation. Give the infusion at a rate of about 60-70 drops/minute.

3. After surgery the patient should receive small frequent feedings (50-75 Gm. of carbohydrate) every 3-4 hours covered with (15-25 units of crystalline zinc insulin subcut. before the meal. These small feedings are continued until normal nutrition can be reestablished.

4. If gastrointestinal surgery has been performed and the patient cannot take food by mouth, nutrition can best be maintained by parenteral methods, give 1 L. of 5% glucose in 5% amino acid solution I.V. slowly over a period of 4 hours. This should be covered with 15-40 units of crystalline zinc insulin subcut. before beginning the infusion. Three L./day is an average requirement. This therapy may be continued until oral nutrition can be resumed.

Shuman, C.R.: Management of diabetes mellitus in patients undergoing surgery. *J.A.M.A.* 155:621-6, 1954.

## ORGANIC HYPERINSULINISM

### Essentials of Diagnosis

- Sudden hunger and weakness, with sweating, pallor, paresthesias, and personality changes
- Tremor, paralysis, convulsions
- Low fasting blood glucose with attacks and prompt response to administration of glucose.

Differentiate from other causes of hypoglycemic attacks, e.g., hepatic disease, adrenal or pituitary insufficiency, and from the more common functional hypoglycemia. Distinguish also from neurotic and psychotic disorders, brain tumors, cerebrovascular accidents, and especially from psychomotor epilepsy.

### General Considerations.

Hyperinsulinism is most commonly due to an adenoma of the islets of Langerhans; at times these may be multiple and small and may escape detection. A few become malignant with functional metastases. More rarely, and almost always only in children, there is primary hypertrophy and hyperplasia of all islets rather than a single adenoma. Adenomas may be familial, and may be associated with adenomas of the parathyroids and of the pituitary. In rare instances tumors in other organs than the

pancreas may produce a picture indistinguishable from that of the insulinomas.

The signs and symptoms are those of acute and chronic hypoglycemia, the disease may progress to permanent and irreversible brain damage. Although the adenoma is more commonly located in the tail and body, the head of the pancreas may also be the site.

### Clinical Findings.

Whipple's triad consists of (1) a history of attacks of hunger, weakness, sweating, and paresthesias coming on during the fasting state, (2) a fasting blood glucose level of 40 mg./100 ml. or less during attacks, and (3) immediate recovery upon administration of glucose. There is a history of previous good health but an intolerance to exercise in the fasting state.

**A Symptoms and Signs** Premonitory manifestations (mostly vasomotor) may include sudden hunger and weakness, especially in the fasting state, headache or faintness, vertigo, sweating, paresthesias of the face, lips, or tongue, visual disturbances, and tremors or palpitation. CNS changes may appear, including vomiting, diplopia, and ataxia, and hypaesthesias, aphasia, twitches and rigor, paralysis, convulsions, or coma. Personality and mental changes vary from anxiety or exhilaration to severe psychotic states, often mistaken for alcoholism or catatonia. Patients with long-standing hyperinsulinism are obese as a result of chronic high-carbohydrate intake.

**B Laboratory Findings** The fasting blood glucose is low, and the glucose tolerance curve is low or may have a sharp fall to low levels in 2-5 hours, with no spontaneous return to normal. These findings are not of great diagnostic value except to differentiate organic hyperinsulinism from functional hyperinsulinism.

Insulin tolerance is variable, and the patient may show resistance to insulin, whereas in adrenal and pituitary insufficiency the patient is sensitive to insulin. Epinephrine causes a variable rise in blood glucose which does not occur in severe liver disease.

### C. Special Tests:

1. Prolonged fasting - The patient receives no food and only water or black coffee with saccharin for up to 72 hours. During this time he exercises mildly. In almost all patients with islet cell adenoma on this regimen the blood glucose will fall to below 30 mg./100 ml. and the symptoms of hypoglycemia will be produced.

2 **Orinase<sup>®</sup> tolerance test** - One Gm of sodium tolbutamide (Orinase<sup>®</sup>) is injected I V in 20 ml of physiologic saline solution. In patients with islet cell adenoma the blood glucose falls to 50-80% of the fasting level in 30 minutes and remains low for several hours, whereas in nonorganic or functional hyperinsulinism the blood glucose level falls to hypoglycemic levels and then rises to normal levels in 1-2 hours. This rapid screening test is not without danger and at times must be interrupted by the administration of I V glucose to prevent severe convulsions and coma.

#### **Differential Diagnosis** (See table on p 562)

The most important differentiation is that between organic and functional hyperinsulinism. Other disorders which must be distinguished are rarer causes of hypoglycemia (e.g., renal glycosuria), neurotic and psychotic disorders, hysteria, epilepsy and brain tumor, acute and chronic alcoholism, cerebrovascular accident, peptic ulcer, and bizarre neuromuscular disorders. Always make sure that the patient has not been taking insulin. In children, differentiate from galactosemia, Von Gierke's disease and hypoglycemia associated with leucine sensitivity. In adults large retroperitoneal sarcomas may give rise to a clinical picture similar to that of hyperinsulinism. Spontaneous hypoglycemia may at times precede the onset of diabetes mellitus.

#### **Complications**

Complications become more important the longer hypoglycemia persists. Retinal and cerebrovascular hemorrhages may occur. Coronary insufficiency and paroxysmal tachycardia may be precipitated by hypoglycemia. Repeated attacks may lead to progressive neuropathy and myelopathy with irreversible damage, causing foot drop, muscle atrophy and pyramidal signs. Permanent personality changes and even mental defects secondary to hydrocephalus have been observed; these changes may occur even after successful surgical treatment. After surgery transient or even permanent diabetes mellitus may occur if too much pancreatic tissue has had to be removed; pancreatic insufficiency may ensue. Fistulas from the pancreas to the skin are not rare. If symptoms recur after an adenoma has been removed, multiple adenomas must be considered.

In any case of organic hyperinsulinism it must be remembered that parathyroid and pituitary adenomas are often associated with islet cell adenomas and that gastric ulceration is frequently present as well. This syndrome may be familial (syndrome of multiple adenomatosis).

#### **Treatment**

**A Emergency Treatment** - Treat as for hypoglycemic reaction due to insulin overdosage (see p 557).

#### **B General Measures**

1 **Corticotropin (ACTH)** or the cortisones - The administration of these drugs (for their hyperglycemic effect) has been shown to be of considerable benefit in the management of some children suffering from this condition. In adults these drugs have not been as effective.

2 **Diet** - Dietary management will usually fail in organic hyperinsulinism and in severe liver failure (hepatogenic hypoglycemia). However, a diet should be tried. The diet is low in carbohydrates in order to avoid stimulation of the pancreas to elaborate insulin. Rapidly utilized carbohydrates are replaced by slow-acting ones (e.g., 3 and 7% vegetables, 10-15% fruits, and bananas). Protein is an important source of slowly-liberated carbohydrate which apparently has less stimulating effect on the pancreas and is useful in supplying added calories.

The diet is best divided into 6 or more meals a day. It may be necessary to feed the patient at regular intervals throughout the 24 hour period. If the hypoglycemia is as severe as this, it is advisable not to prolong medical therapy but to prepare the patient properly for surgery.

3 **Sedation** - Phenobarbital 15-30 mg (¼ 1/2 gr) q i d may be valuable in reducing neuromuscular irritability.

4 **Restriction of physical activity** - Exercise increases the utilization of glucose; there by exaggerating the effect of excess insulin. If exercise is unavoidable, such activity should be preceded by supplementary carbohydrates.

5 **Identification card** - Patient should carry a bracelet or card similar to that used by a diabetic (see p 557).

6 **Emergency carbohydrates** - The patient should carry a small supply of rapidly-available carbohydrate (candy, lumps of sugar) at all times. He is to avoid taking these except when definitely indicated.

**C Surgery** - Complete excision of hyperplastic or adenomatous islet tissue is indicated when this is found to be the cause. At times total pancreatectomy is required. The tumors may be in ectopic sites.

#### **Prognosis**

If hyperinsulinism is diagnosed early and cured surgically, complete recovery is likely. Medical therapy with corticotropin or cortisone is not very effective in long-term treat-



ment, but has been used successfully in children, in whom the disease may be transient, in the preoperative phase, and in rare cases when tumors cannot be located or surgery is refused. Brain damage usually is not reversible in spite of removal of the tumor. Operation may cure the patient even if the tumor has been present for several years, since the incidence of malignancy is low and metastases occur late. The prognosis is worse in children and in the elderly, who are ill-equipped to handle sudden changes in glucose.

Fajans, S.S., Schneider, J.M., & J.W. Conn. The diagnostic value of sodium tolbutamide in hypoglycemic states. *J. Clin. Endocrinol.* 21:371-86, 1961.

Joslin, E.P., & others: *The Treatment of Diabetes Mellitus*, 9th ed. Lea & Febiger, 1952.

## DISEASES OF THE TESTES

### MALE HYPOGONADISM

Male hypogonadism may be classified according to time of onset, i.e., prepuberal, puberal (Klinefelter's syndrome), or postpuberal. Eunuchism implies complete failure of gonadal development, eunuchoidism implies only partial deficiency.

The etiologic diagnosis of hypogonadism (e.g., primary or secondary) is usually based on laboratory tests.

Type of Hypogonadism	Urinary 17-Ketosteroids	Urinary Gonadotropins
Primary	Low or normal	Elevated
Secondary		
Pituitary	Usually low but may be normal	Very low
Anorexia nervosa	Low or normal	Low normal. Not generally as low as pituitary type.
Thyroid (tertiary?)	Low or normal	Low

### 1. PREPUBERAL HYPOGONADISM

The diagnosis of hypogonadism should not be made in boys under the age of 17 or 18, since it is difficult to differentiate from "physiologic" delay of puberty.

Prepuberal hypogonadism is most commonly due to a specific gonadotropic deficiency of the pituitary. It may also occur as a result of destructive lesions near the pituitary region (e.g., suprasellar cyst) or, more rarely, as a result of destruction or malformation of the testes themselves (prepuberal castration).

In cases associated with a complete pituitary defect, the patient is of short stature or fails to grow and mature. Otherwise the patient is strikingly tall due to overgrowth of the long bones. The external genitalia are underdeveloped, the voice is high-pitched, the beard does not grow, and the patient lacks libido and potency and is unable to tan. In adult life he presents a youthful appearance, with obesity (often in girdle distribution), disproportionately long extremities (span exceeds height), lack of temporal recession of the hairline, and a small Adam's apple. Gynecomastia is occasionally seen (but apparent gynecomastia may be merely fat). The skin is fine-grained, wrinkled, and sallow, especially on the face. The penis is small and the prostate undeveloped. Pubic and axillary hair are scant. The testes may be absent from the scrotum (cryptorchism) or very small. Spermatogenesis does not occur.

Bone age is retarded. Skull x-rays may show a lesion of the sella or above the sella (e.g., craniopharyngioma). Anemia may be present. Urinary 17-ketosteroids are low or normal in testicular failure, very low or absent in primary pituitary failure. Urinary FSH is absent in primary pituitary failure, elevated in castration or testicular failure.

Determination of the genetic chromosomal type may reveal anomalies, e.g., hermaphroditism.

The response to chorionic gonadotropin injections in cases due to pituitary failure will be maturation, rise of urinary 17-ketosteroids, and occasionally descent of cryptorchid testes, in primary testicular failure no such response occurs. Testicular biopsy shows immature tubules and Leydig cells.

Adequate testosterone therapy (see p. 580), can make these individuals into apparently nor-

mal adult males except that they cannot produce sperm. These patients must be placed on testosterone and maintained for life on adequate doses of testosterone. There is little evidence that any pituitary substance or gonadotropin is of significant value in treating primary hypogonadism. Long acting testosterone preparations 200-300 mg 1 M every 2-4 weeks may be employed (see p. 580). An alternative method of oral administration of other androgens (see p. 580) entails all the difficulties of prolonged oral administration. Dosage varies with different patients but 10-25 mg of methyl testosterone daily orally is usually adequate to cause and maintain maturation and virilization. There is no great advantage of buccal over oral administration.

## 2 PUBERAL HYPOGONADISM (Klinefelter's Syndrome)

The outstanding example of this group of diseases is the so called Klinefelter's syndrome (puberal seminiferous tubule failure). It is a genetic disorder which is recognized at or shortly after puberty. It is at times familial. A similar acquired syndrome has been ascribed to infection. Most commonly there is only failure of the tubules and lack of the testicular estrogen like hormone with permanent sterility. The secretory function of the Leydig cells ranges from normal to definite failure. Study of the chromosomal pattern shows that the majority of these patient's cells are chromatin positive.

The clinical findings are swelling of the breasts (gynecomastia), sterility, lack of libido and potency (rare) and at times lack of development of body hair and female escutcheon. Skeletal and muscular development are usually normal. There may be associated mental retardation. The testes are usually small but are larger than in prepuberal hypogonadism. The penis and prostate are usually normal. The ejaculate contains no spermatozoa. Urinary 17 ketosteroids are low normal or normal. Urinary FSH is elevated (the most significant finding). Testicular biopsy shows sclerosis of the tubules, nests of Leydig cells and no spermatozoa. The chromatin count is most commonly XXY (rarely XXXY or mosaic) with a chromatin positive buccal smear. Bone age may be delayed.

All causes of gynecomastia must be differentiated from Klinefelter's syndrome. Including simple gynecomastia of puberty, liver disorders, chorio epithelioma, estrogen produc-

ing tumors and obesity with small genitalia. The urinary FSH and the testicular biopsy will settle the diagnosis.

A similar picture is at times associated with myotonia dystrophica.

No treatment is necessary unless lack of potency is a problem. In which case testosterone should be given as for prepuberal hypogonadism. If gynecomastia is disfiguring, plastic surgical removal is indicated.

Grumbach M M & M L Barr. Cytologic tests of chromosomal sex in relation to sexual anomalies in man. Recent Prog Hormone Res 14:255-334, 1958.

## 3 POSTPUBERAL HYPOGONADISM

Any pituitary lesion (e.g. tumor, infection, necrosis) will lead to lack of gonadotropin. Often hypogonadism is an early sign. The testes may be damaged by trauma, x-ray irradiation, infection or in other ways. States of malnutrition, anemia and similar disorders may lead to functional gonadal underactivity. The male climacteric, although a somewhat disputed syndrome, probably does exist. It makes its appearance about 20 years later than the female menopause.

The symptoms are varying degrees of loss of libido and potency, retardation of hair growth, especially of the face, vasomotor symptoms (flushing, dizziness, chills), lack of aggressiveness and interest, sterility and muscular aches and back pain. Atrophy or hypoplasia of external genitalia and prostate is rare. The skin of the face is thin, finely wrinkled and sallow colored and the beard is scant. Hair is absent on the antitragus of the ear (Hamilton's sign). Girdle type obesity and kyphosis of the spine are present.

Urinary 17 ketosteroids are low. Urinary FSH may be normal but is low in cases due to pituitary lesions and elevated in true testicular failure. The sperm count is low or spermatozoa may be absent. Bone age is usually normal but the skeleton may show epiphyseal dysplasia especially of the vertebral column (Scheuerman's disease) and osteoporosis.

True adult hypogonadism must be differentiated from the far more commonly seen psychogenic lack of libido and potency. Confusion may also arise in men who are obese and have a sparse beard and small genitalia but normal sperm counts and urinary androgens (fertile eunuchs). These patients may represent examples of end organ unresponsiveness and are not helped by treatment.

Oral methyltestosterone (see p 580) is highly effective. The dosage necessary to control symptoms and to aid in overcoming the protein loss and debility of age is often as low as 5-20 mg. daily. This dose may be used for a short period of time to control symptoms or may be continued indefinitely for control of symptoms and for its protein anabolic effect. The use of the long-acting testosterone by injection may be more practical for prolonged treatment.

#### Prognosis of Hypogonadism.

If hypogonadism is due to a pituitary lesion, the prognosis is that of the primary disorder (e.g., tumor, necrosis). The prognosis for restoration of virility is good if testosterone is given. The sooner administration is started, the fewer stigmas of eunuchoidism remain (unless therapy is discontinued).

The prognosis for fertility is usually not good. It is only feasible in the instances where the testicular elements are present but are unstimulated due to lack of pituitary tropic hormones. This therapy is not very practical.

Minor forms of hypogonadism may be corrected by proper nutrition, by the use of thyroid hormone, and by general hygienic measures.

Cryptorchism should be corrected surgically early, since the incidence of malignant testicular tumors is higher in ectopic testicles and the chances for ultimate fertility is lessened in long-standing cases.

Kaplan, N. M., & R. G. Norfleet: Hypogonadism in young men (with emphasis on Klinefelter's syndrome) *Ann. Int. Med.* 54 461-81, 1961

#### MALE HYPERGONADISM & TESTICULAR TUMORS

In adults, almost all lesions causing male hypergonadism are functioning testicular tumors, which quite frequently are malignant. In children, male hypergonadism may take the form of true precocious puberty, due to pituitary or hypothalamic lesions, or pseudoprecocious puberty, due to lesions of the testes or adrenal glands.

#### 1. PREPUBERAL HYPERGONADISM

##### Sexual Precocity Along Isosexual Pattern

Types and Causes	Characteristics
Neurogenic Brain tumor Encephalitis Congenital defect with hypothalamic involvement Pituitary idiopathic activation, "constitutional type"	Testes mature normally, spermatogenesis occurs, secondary characteristics normal, sex hormones excreted in normal adult amounts
Gonadal Interstitial cell tumor of testis	Tumor in one gonad, the other gonad immature or atrophic, spermatogenesis does not occur, sex hormones excreted in excessive amounts.
Adrenal Embryonic hyperplasia or tumor	Testes usually small and immature, occasionally containing aberrant adrenal tissue, no spermatogenesis, often results in adrenocortical insufficiency in males

The symptoms and signs are premature growth of pubic and axillary hair, beard, and external genitalia and excessive muscular development. In true precocity due to pituitary or hypothalamic lesions the testicles enlarge as well and spermatogenesis occurs. In adrenal virilization or testicular tumor there is testicular atrophy, with or without palpable nodules, spermatogenesis does not take place. In childhood, interstitial cell tumors are the principal testicular tumors to be considered. Bilateral interstitial cell nodules are also seen with adrenal hyperplasia.

If the cause of precocity is 'constitutional,' it is usually a harmless disorder, although the sex activities of these children must be controlled to prevent socially undesirable conceptions. If precocity is due to hypothalamic or pituitary lesions, the prognosis is poor since most of these tumors are not removable. Adrenal tumors and testicular tumors are often malignant.

Most patients with this syndrome who survive into adulthood will be short as a result of premature maturation and closure of their epiphyses.

**Treatment.**

In cases where the tumor is accessible, surgical removal is the treatment of choice. Bilateral adrenal hyperplasia which causes pseudoprecocious puberty can be successfully treated with cortisone, and normal development and spermatogenesis will occur following treatment. The use of progesterone preparations (e.g., Depo Provera<sup>®</sup>) in the treatment of sexual precocity is under investigation.

Wilkins, L. The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, 2nd ed. Thomas, 1957

Wilkins, L. Variations in pattern of adolescent development Chap 10 in The Diagnosis, etc. See above

Wilkins, L. Precocious sexual development Chap 11 in The Diagnosis etc. See above

**Characteristics of Testicular Tumors**

Tumor and Hormone	Clinical Manifestations
Seminoma Elevation of urinary FSH	Onset usually at age 30-50 Tumor radiosensitive No endocrinologic manifestations
Teratoma No hormone elaborated except in mixed tumors	May occur in childhood also No endocrinologic manifestations unless the tumor is of a mixed type Tumor radio-resistant invasive.
Chorio-epithelioma Chorionic gonadotropin elevated, Aschheim-Zondek test positive	Rare Gynecomastia Tumor rapidly invasive and metastasizing radioresistant. Leydig cells overactive due to stimulation by tumor
Leydig cell 17 ketosteroids elevated	Very rare. Occurs at any age and causes virilization At times bilateral often multiple.
Sertoli cell and tubular adenoma of Pick may elaborate estrogens	Benign tumors, probably developmental rests Associated with congenital anomalies of genital tract. Rarely feminizing

Dean, A. L. The treatment of testes tumors.  
J Urol 76 439-46, 1956

## 2. NEOPLASMS OF THE TESTES IN ADULTS

### (Postpubertal Hypergonadism)

Many or most testicular neoplasms are functioning (i.e., productive of androgenic or estrogenic hormones), and the majority are highly malignant (see table opposite). They are at times quite small, and are clinically recognized because of their hormonal effects or because of the presence of metastases. In general, once hormonal manifestations have become pronounced, cure by surgical removal is very unlikely. Some tumors are bilateral, e.g., interstitial cell tumors. Often a mixed picture is present.

The incidence of malignancy in cryptorchidism is high.

**Treatment.**

If the diagnosis is made early, surgical removal may be curative, radiotherapy is feasible as a palliative measure in radiosensitive types. Chemotherapy may control the growth of chorio-epitheliomas.

**DISEASES OF THE OVARIES****1. FEMALE HYPOGONADISM**

The outstanding symptom of female hypogonadism is amenorrhea (see below). Partial deficiencies principally corpus luteum failure may occur which do not cause amenorrhea but anovulatory periods or metrorrhagia.

Estrogenic failure has far-reaching effects especially if it begins early in life (e.g., Turner's syndrome).

Primary pituitary disorders are much less common causes of hypogonadism in the female than primary ovarian disorders, and are almost always associated with other signs of pituitary failure.

Ovarian failure starting in early life will lead to delayed closure of the epiphyses and retarded bone age, often resulting in tall stature with long extremities. On the other hand in ovarian agenesis, dwarfism is the rule (see below). In adult ovarian failure, changes are more subtle, with some regression of secondary sex characteristics. In estrogenic deficiency of long standing in any age group, osteoporosis, especially of the spine, is almost al-

ways found since estrogen is a potent stimulus of osteoblasts.

A relatively rare form of ovarian failure is seen in states of androgenic excess, usually derived from the adrenal cortex, when estrogens, though present in the body, are suppressed by the presence of large amounts of androgens (see Virilizing Disorders of the Ovary, p 574).

## AMENORRHEA

Since regular menstruation depends upon normal function of the entire physiologic axis extending from the hypothalamus and pituitary to the ovary and the uterine lining, it is not surprising that menstrual disorders are among the most common presenting complaints of endocrine disease in women. Correct diagnosis depends upon proper evaluation of each component of the axis, and nonendocrine factors must also be considered.

If normal menstruation is defined as shedding of endometrium which has been stimulated by estrogen or by estrogen and progesterone which is subsequently withdrawn, it is obvious that amenorrhea can occur either when hormones are deficient or lacking (the hypohormonal or ahormonal type) or when these hormones, though present in adequate amounts are never withdrawn (the continuous hormonal type).

Primary amenorrhea implies that menses have never been established. This diagnosis is not usually made before the age of about 18. Secondary amenorrhea means that menses once established have ceased (temporarily or permanently).

The most common type of hypohormonal amenorrhea is the menopause, or physiologic failure of ovarian function. The most common example of continuous hormonal amenorrhea is that due to pregnancy, when cyclic withdrawal is prevented by the placental secretions. These 2 conditions should always be considered before extensive diagnostic studies are undertaken.

The principal diagnostic aids which are used in the study of amenorrhea are as follows (1) vaginal smear for estrogen effect, (2) endometrial biopsy, (3) "medical D and C" (see below); (4) BBT determination, (5) urine determinations of 17-ketosteroids, FSH, and pregnandiol, (6) culdoscopy and gynecography, and (7) chromosomal studies (e.g., buccal or vaginal smear).

## 1. PRIMARY AMENORRHEA

Most cases of primary amenorrhea are of the hypohormonal or ahormonal type. Exact diagnosis is essential to rule out organic lesion along the hypothalamic-pituitary-gonadal axis. The chromosomal sex pattern must be determined in all cases.

The causes are as follows.

(1) Hypothalamic causes. Constitutional delay in onset, debility, serious organic illness.

(2) Pituitary causes (with low or absent urinary FSH) Suprasellar cyst, pituitary tumors (eosinophilic adenomas, chromophobe adenomas, basophilic adenomas), isolated lack of pituitary gonadotropins

(3) Ovarian causes (with high urinary FSH): Ovarian agenesis (Turner's syndrome), destruction of ovaries (e.g., due to infection), "premenarchal menopause"

(4) Uterine causes (usually with normal urinary FSH) Malformations, imperforate hymen, hermaphroditism, unresponsive or atrophic endometrium.

(5) Miscellaneous causes. Adrenal virilism, 17 $\alpha$ -pseudohermaphroditism (with high urinary 17-ketosteroid and pregnandiol levels), various androgenic tumors.

### Treatment.

Treatment is similar to that of secondary amenorrhea (see below). The underlying organic cause should be corrected if possible. If secondary sex characteristics have not developed, estrogens alone may be of value.

## 2. SECONDARY AMENORRHEA

Temporary cessation of menses is extremely common and does not require extensive endocrine investigation. In the childbearing age, pregnancy must be ruled out. In women beyond the childbearing age, menopause should be considered first. States of emotional stress, malnutrition, anemia, and similar disorders may be associated with temporary amenorrhea, and correction of the primary disorder will usually also reestablish menses.

By the use of the "medical D and C" (see p 582), i.e., the administration of progesterone with subsequent withdrawal, these amenorrheas can be arbitrarily divided into amenorrhea with negative D and C, and amenorrhea with positive D and C. The former (with the exception of pregnancy) show an atrophic ov.

hypoestrin type of endometrium, the latter show an endometrium of the proliferative type but lacking progesterone.

(1) Secondary amenorrhea with negative medical D and C may be due to the following causes: Pregnancy (Aschheim-Zondek test positive), menopause (urinary FSH elevated), pituitary tumor, pituitary infarction (Sheehan's syndrome), virilizing syndromes such as arrhenoblastoma, Cushing's disease, Addison's disease, and miscellaneous causes such as anorexia nervosa, profound myxedema, irradiation of the uterine lining, and hysterectomy.

(2) Secondary amenorrhea with positive medical D and C may be due to the following causes: Metropathia hemorrhagica Stein-Leventhal syndrome, estrogen medication, estrogenic tumors, i.e., granulosa cell tumors (rare), hyperthyroidism, and perhaps liver disease.

Some degree of overlap in these two groups is sometimes found.

#### Treatment.

The aim of therapy is not only to reestablish menses (although this is valuable for psychologic reasons) but also to attempt to establish the etiology (e.g., pituitary tumor) of the amenorrhea and to restore reproductive function.

Treatment depends upon the underlying disease. It is not necessary to treat all cases, especially amenorrhea or irregular menses in unmarried girls or women. These cases usually are corrected spontaneously after marriage or first pregnancy.

In patients whose response to progesterone is normal, the administration of this hormone during the last 10-14 days of each month, orally or parenterally (see p. 582), will correct the amenorrhea.

In patients who are unresponsive to progesterone and whose urinary gonadotropin levels are low, treatment of a pituitary lesion may restore menstruation. Gonadotropins would appear to be of value, and human pituitary FSH has been used with some success experimentally. However, in current clinical practice, estrogen alone or in combination with progesterone (see p. 581) is more commonly used. If urinary gonadotropins are high, gonadotropins are of no value, treatment with estrogens alone or with estrogens and progesterone (see p. 581). Cortisone may restore menstruation in certain virilizing disorders.

General measures include dietary management as required to correct overweight or underweight, psychotherapy in cases due to emotional disturbance, and correction of ane-

mia and any other metabolic abnormality which may be present (e.g., mild hypothyroidism).

Rogers, J.: *Menstruation and systemic disease*. New England J. Med. 259:676-81, 721-7, and 770-5, 1958.

### 3. HYPOTHALAMIC AMENORRHEA

Secondary hypothalamic amenorrhea, due to emotional or psychogenic causes, is far more common in young women than amenorrhea due to organic causes (except for pregnancy). It is probably mediated by a hypothalamic block of the release of pituitary gonadotropic hormones, especially LH. Pituitary FSH is still produced and is found in normal or low levels in the urine. Since some LH is necessary in the production of estrogen as well as FSH, a state of hypoestrinism with an atrophic endometrium will eventually result.

A history of psychic trauma just preceding the onset of amenorrhea can usually be obtained. The urinary FSH level is normal or low normal, and the 17-ketosteroid level is low normal. Vaginal smear and endometrial biopsy show mild hypoestrin effects. The response to progesterone (medical D and C) is variable. The endometrium responds to cyclic administration of estrogens.

Menses often return spontaneously or after several induced 'cycles.' Psychotherapy is of the greatest value. If amenorrhea persists, signs of severe estrogen deficiency will appear and must be treated.

It is most important to recognize this syndrome and not to mistake it for an organic type of amenorrhea with a very different prognosis.

#### TURNER'S SYNDROME (Primary Ovarian Agenesis, Gonadal Dysgenesis)

Turner's syndrome is a rather rare disorder due to congenital absence of the ovaries and associated with dwarfism and other anomalies. Evidence suggests that in most instances patients with this syndrome lack one of the 2 X chromosomes. A rarer variant shows androgenic tissue in the gonadal remnant with mild virilization.

The principal features include congenital ovarian failure, genital hypoplasia with infantile uterus, vagina, and breasts and primary amenorrhea, scant axillary and pubic hair,

short stature, usually between 122-142 cm. (48-56 inches), increased carrying angle of arms, webbing of neck (quite common), eye disorders, stocky "shield" chest, cardiovascular disorders, especially coarctation of the aorta, congenital valve defects, osteoporosis with increasing age, and prematurely senile appearance. Nevii are common. Idiopathic edema is seen in infants.

Urinary FSH is high, and 17-ketosteroids are low. Bone age is retarded. The chromatin sex pattern most often shows a "negative" buccal smear and XO chromosomal pattern.

Exploratory operation shows a "streak ovary" and, at times, islands of interstitial cells.

The principal disorder to be differentiated is pituitary dwarfism. In this disorder the urinary FSH is low or absent and other signs of pituitary failure are present. The axillary and pubic hair is absent in pituitary dwarfs, although it is scant in Turner's syndrome. It increases with estrogen administration. Other forms of constitutional dwarfism, such as Laurence-Moon-Biedl syndrome, are ruled out by the urinary FSH and lack of stigmas such as polydactylia, and the presence of retinitis pigmentosa and other signs of the disease. The short stature and occasional metacarpal deformities may resemble pseudohypoparathyroidism, but these patients menstruate normally.

With the administration of estrogens some increase in height can be achieved, but this is almost never enough to increase stature significantly. Androgens may also promote growth.

If untreated, growth will eventually cease since the epiphyses will close spontaneously (though late). The administration of estrogen will develop the breasts and uterus and lead to anovulatory menses upon cyclic withdrawal. Fertility can never be achieved.

The associated congenital cardiovascular anomalies may cause early death or may require surgical correction (e.g., coarctation). Webbing of the neck can be corrected by plastic surgery.

Several variants of this syndrome with different chromosomal patterns have been recently described.

Jacobs, P., & others. Abnormalities involving the X chromosome in women. *Lancet* 1. 1213-6, 1960.

## MENOPAUSAL SYNDROME

### Essentials of Diagnosis

- Menstrual irregularities associated with hot flushes and personality changes
- Age 45-55 years (unless due to surgery or irradiation)
- Hypoestrogen vaginal smear, urinary FSH elevated, osteoporosis in later years

The personality changes and flushes must be differentiated from those due to anxiety states, hyperthyroidism, or pheochromocytoma, the menstrual disorders must be distinguished from primary ovarian or uterine lesions (e.g., tumors) and other endocrine disorders (e.g., of the thyroid, adrenal, pituitary).

### General Considerations

The term "menopause" refers to the permanent or final cessation of menstrual function either as a normal physiologic event or as a result of surgery or ovarian irradiation. In a broader sense the "menopausal syndrome" includes all of the sequelae of permanent cessation of ovarian function, of which the absence of menstruation is only a part.

The majority of women go through physiologic menopause at about 45-50 years of age, but premature ovarian failure may occur before the age of 30. Early menopause is more common in women who have had an infection or surgical disorder of the genital tract.

The onset of the menopause is often a familial trait.

The surgical or x-ray menopause differs from the natural menopause in its more abrupt onset and the greater severity of manifestations.

The earlier ovarian failure takes place, the more severe are the effects on certain structures, principally the skeleton.

The clinical diagnosis of the menopause is at times difficult, since psychologic factors often overshadow symptoms due to hormonal deficiency. It is also of interest that many women never show any evidence of the menopause, whereas others suffer severely and may even develop psychoses.

Treatment must be directed at the immediate symptoms, but at times - and especially if postmenopausal osteoporosis is present - it must be maintained for prolonged periods.

Although reproductive function ceases, sexual activity past the menopause is not impaired unless psychic factors and misinformation produce an emotional block.

### Clinical Findings

**A Symptoms and Signs.** Amenorrhea is frequently preceded by menometrorrhagia or oligomenorrhea. Hot flushes are often severe, lasting only a few minutes but recurring frequently. The patient complains of feelings of tension, especially fullness in the head. Weight gain and nervous instability with depression, exhilaration, or lassitude are often present. Various aches and "rheumatic pains" commonly occur. Sexual changes include dyspareunia, loss of libido, or in some cases increased sexual interest. The breasts may be painful. Bladder irritation is common.

There are very few objective findings. Mild hypertension, mild hirsutism, tenderness of the spine, and dry skin with coarsening of the hair may occur.

**B Laboratory Findings.** A hypoestrian type vaginal smear and an elevated urinary FSH level (80 mouse units or above) are the only laboratory findings, but they may be quite delayed in their appearance.

**C X-ray Findings.** X-ray may show osteoporosis of the spine in later years.

### Differential Diagnosis.

Since most of the manifestations of the menopausal syndrome are purely subjective, it is often difficult to make an exact diagnosis unless a trial of estrogenic (or androgenic) therapy gives striking relief. The most difficult differentiation is from anxiety states with features of reactive depression. Pheochromocytoma and hyperthyroidism must also be considered. A variety of causes of back pain, including osteoarthritis and rheumatoid arthritis, may be considered in the differentiation from pain due to osteoporosis and menopausal arthralgia. In hypothyroidism menstrual irregularities, emotional changes, and aches and pains are common also. One must make certain that ovarian or uterine neoplasm is not the cause of the menstrual irregularity and back pains.

### Complications.

The serious complications of the menopause are psychosis and, in long-standing cases, osteoporosis. Diabetes mellitus may appear with the menopause. Senile vaginitis may also occur. The postmenopausal patient is more susceptible to degenerative cardiovascular disease and gout.

### Treatment.

#### A. Natural Menopause.

**1. Physiologic aspects (estrogen therapy).** If cycles are very irregular and the patient suffers from menopausal symptoms, begin estrogens about 5 days after the onset of the last menstrual period and continue in a cyclic fashion. Give ethinyl estradiol, 0.05 mg., diethylstilbestrol, 0.5-1 mg., or estrone sulfate, 1.25 mg. by mouth daily except for the first five days of each month. This is simple for patients to remember.

If the patient has become amenorrheal, there is no reason to give estrogens in doses large enough to reinstitute menses but only to control symptoms. This is not always possible.

The duration of therapy has not been standardized and must be adjusted to the individual case. Three months to one year usually suffices, but in some cases therapy may have to be continued over prolonged periods.

Because of the anabolic effect of estrogens and because of their known beneficial effects on bone metabolism and on blood vessels, estrogen therapy has been recommended for life for women beyond the menopause. The advisability of this practice remains unsettled. If a patient is on long-term estrogen therapy she should keep an accurate record of her dosage schedule and bleeding. Whenever bleeding occurs that is not on schedule (during the withdrawal phase), tumor should be suspected. *Note:* Vaginal cytologic examination for pelvic malignancy should be done routinely once or twice a year.

**2. Psychologic aspects.** Many of the symptoms of the menopause are undoubtedly psychologic. The most common symptom is anxiety, more severe emotional disorders may occur. The most serious is involuntal psychotic reaction (see p. 493), or involuntal melancholia. Sedative drugs may be of value (see p. 502). Simple explanation and reassurance that their lives need not be changed because of the menopause are adequate in most patients. In more severe cases the aid of a psychiatrist may be necessary.

**B. Surgical and X-ray Menopause.** These cases differ from the natural menopause only in the abruptness and severity of the symptoms. In these patients it is advisable to help the patient live as normal a life as possible. If normal periods cannot be reinstituted but the patient understands that her sexual function will continue unchanged, she usually makes a suitable adjustment. Estrogen therapy is as for natural menopause (see above).

#### C. Treatment of Complications

**1. Osteoporosis** is discussed on p. 534.



2. Senile vaginitis - Give oral diethylstilbestrol or other estrogens (see p 581) daily. Diethylstilbestrol vaginal suppositories containing 1 mg. may be used daily for 10-14 days while continuing oral diethylstilbestrol. Dienestrol vaginal cream is often helpful

#### Prognosis.

Most women pass through the menopause without requiring extensive therapy. A short course of estrogen therapy may alleviate their symptoms. Others, however, require prolonged and intensive therapy. The average duration of symptoms is 2-3 years.

Some patients show severe depression (Involuntional melancholia or psychotic reaction, see p 493) and even suicidal tendencies.

Rogers, J. The menopause. New England J, Med, 254 697-704 and 750-6, 1956.

## II. FEMALE HYPERGONADISM

Excesses of ovarian hormones are often encountered during the normal reproductive life of women, and most frequently give rise to irregular or excessive menstrual bleeding and, more rarely, to amenorrhea. Excesses before the age of puberty or after the menopause, however, should be thoroughly investigated since the possibility of malignant lesions is great. Estrogenic excess is more common than progesterone excess, which is seen in pregnancy and in chorio-epithelioma. Other extra-ovarian sources of estrogens are malignant tumors of the adrenals which secrete abnormal amounts of estrogens. Since these tumors usually produce excesses of androgens as well, their hyperestrogenic effects are rarely detectable clinically in the female.

Another cause of hyperestrogenism is the ingestion or other use of hormones (e.g., in face creams)

### PREPUBERAL FEMALE HYPERGONADISM

It is important to differentiate organic lesions of the pituitary-hypothalamic region, which cause true precocious puberty in females, from pseudoprecocity due to granulosa cell tumors and choriocarcinoma. Constitutional true sexual precocity may be partial, consisting only of precocious breast development and early growth of pubic hair, or it may

be associated with premature menarche as well. It is often familial. Albright's syndrome causes true precocity with fibrous dysplasia of bone (osteitis fibrosa disseminata) and pigmentary changes of the skin (see p 88).

Granulosa cell tumors of the ovary cause uterine bleeding by virtue of their estrogenic secretions, but they do not cause ovulation and these girls are not fertile. The same is usually true of choriocarcinoma. Both of these tumors are highly malignant.

Simple follicle cysts of the ovary, at times easily palpable, may cause precocity.

Pseudoprecocious puberty may also be caused by ingestion of estrogens. Thiazolsulfone (Promizole®) occasionally causes early growth of pubic hair.

The significance of the differentiation between true and pseudoprecocious puberty is that in true precocity ovulatory cycles may occur and the patient must be protected from pregnancy. The most useful guide to the differentiation is the urinary FSH determination. Urinary FSH is not present in girls before the age of puberty, even in pseudoprecocious puberty, whereas girls with true precocious puberty may secrete 5-10 mouse units/day.

The diagnosis of either true or pseudoprecocious puberty is important because many cases are due to tumors which must be found and removed if possible. Unfortunately, most estrogen-secreting tumors are highly malignant, and tumors of the third ventricle and other lesions near the hypothalamus are quite difficult to remove.

Precocious development of breasts and early onset of menses usually cause psychic disturbances, which may be severe. Short stature in adult life is the rule since bone age is advanced and the epiphyses close prematurely. As adults these patients may suffer a great deal from excessive menstrual bleeding, which may cause anemia unless it is checked. Cystic mastitis is a chronic problem, and the incidence of uterine adenofibromas is high. It is not definitely known whether long-standing hyperestrogenism causes a higher incidence of breast and genital tract cancer, but it may be a significant aggravating factor.

The only treatment is surgical removal of tumors, but most are malignant and metastasize early. The prognosis for simple constitutional precocity is not so unfavorable, although these girls must be watched to prevent pregnancy. Recent reports on the use of progesterone (Depo Provera®) are encouraging.

Eberlein, W. R., & others. Ovarian tumors and cysts associated with sexual precocity;

report of three cases and review of literature.  
J. Pediat 57 484-97, 1960

### ADULT FEMALE HYPERGONADISM

Adult female hypergonadism may be due to estrogenic excess alone or to combined excess of estrogen and progesterone. Estrogenic excess is characterized by menorrhagia or, rarely, amenorrhea. The vaginal smear shows estrogenic excess. Lack of ovulation is demonstrated by the absence of BBT rise. Sterility is the rule. The medical D and C is positive; a bleeding starts after a short course of progesterone. Endometrial biopsy shows a proliferative endometrium. The urinary FSH level is low.

#### Hormones Elaborated by Actively Secreting Ovarian Tumors

Type	Secretion
Feminizing	
Granulosa cell	Estrogen+++
Theca cell	Estrogen++
Luteoma?	Estrogen+ and/or progesterone
Virilizing*	
Arrhenoblastoma	Androgen+++
Adrenal rest (lipoid cell)	Androgen++ and corticoids
Hilus cell	Androgen+++
Miscellaneous	
Choriocarcinoma	Gonadotropins +++ and estrogens
Dysgerminoma*	Gonadotropins+ and androgens?
Gynandroblastoma	Androgens++ and estrogens+++
Siruma ovarii	Thyroxin+

\*Most women have complete amenorrhea with negative medical D and C since the endometrium is atrophic.

Adult female hyperestrogenism may be caused by (1) metropathic hemorrhagica, in which ovulation does not occur, (2) liver disease, which interferes with the catabolism of estrogens, (3) drug administration (e.g., estrogen creams or tablets), (4) granulosa cell and theca cell tumors (both types are usually present), and (5) Stein-Leventhal syndrome (see at right).

Estrogen and progesterone excess often causes amenorrhea without other evidence of hypogonadism. Excess of both hormones may be due to (1) pregnancy, (2) chorio-epithelioma or teratoma, (3) luteoma, or (4) malignant adrenal tumors (possibly). The medical D and C is negative. Pregnenolol is found in the urine. Secretory endometrium is demonstrated on biopsy. The urinary FSH level (actually chorionic gonadotropin) may be high, and the Aschheim-Zondek test may be positive.

Treatment depends upon the cause. Cyclic administration of progesterone, wedge resection of the ovary, or surgical removal of tumors at times restores normal cyclic ovarian function. Recent reports of treatment with human pituitary FSH are encouraging.

The prognosis is that of the underlying disease. Treatment with progesterone alone or with estrogen in cyclic fashion is usually quite effective in temporary disorders of ovulation. Stubborn anovulation may persist, however, after cessation of therapy.

Israel, S. L., & J. C. Mutch. Endocrinologic effects of certain ovarian tumors. Surg., Gynec. & Obst. 105 166-76, 1957.

### VIRILIZING DISORDERS OF THE OVARY (See also under Adrenal.)

#### Stein-Leventhal Syndrome

The Stein-Leventhal syndrome occurs only in young women. It is characterized by bilaterally enlarged polycystic ovaries, mild hirsutism, obesity, and oligomenorrhea or amenorrhea. Urinary FSH is normal, the medical D and C produces withdrawal bleeding, estrogen is present, and the urinary 17-ketosteroids are present in high normal amounts. At operation the enlarged ovaries are found to have many follicles on the surface and are surrounded by a thick capsule ("oyster ovaries").

Wedge resection often restores ovulatory periods and fertility, but hirsutism is not helped by this procedure. Cortisone administration may be of value in some patients.

#### Diffuse Theca Luteinization

This disorder is similar to the Stein-Leventhal syndrome, but many follicles are not found in the ovaries. Hirsutism and often mild virilization are associated with amenorrhea.

## HORMONES & HORMONE-LIKE AGENTS

### ANTERIOR PITUITARY HORMONES

All of the anterior pituitary hormones are protein substances and must therefore be administered parenterally to be effective, if taken by mouth they are digested by the digestive enzymes. In general, with the exception of the growth and lactogenic hormones, whose effects are not mediated directly through other glands, the anterior pituitary hormones appear to have a regulatory function on the other glands of internal secretion. The anterior pituitary in turn is probably regulated to a great extent by a hypothalamic-pituitary pathway.

Several of these hormones have been prepared in "pure" or "almost pure" form: adrenocorticotropin (ACTH, corticotropin), growth, lactogenic (luteotropic), follicle-stimulating (FSH), interstitial cell-stimulating (luteinizing), and thyroid-stimulating (TSH) hormones. There may be other factors in the anterior pituitary, but they have not yet been fully identified. Of the pure preparations only corticotropin and thyrotropin are at present commercially available.

#### Corticotropin (ACTH). (See p 583)

Corticotropin has been shown to have remarkable effects in arresting many disease processes which are not satisfactorily influenced by other therapeutic agents. Its effect is entirely mediated by the stimulation of the adrenal cortex. Corticotropin is a protein of small molecular size and certain peptides derived from it have been found to have similar and as marked physiologic effects as the hormone itself.

**A Metabolic Effects in Humans.** ACTH in adequate doses in normal human beings produces the following metabolic effects: Increased excretion of nitrogen, potassium, and phosphorus; retention of sodium and secondary retention of water; elevation of fasting blood glucose and diabetic glucose tolerance curve; and increased urinary excretion of uric acid, calcium, 17-ketosteroids, and corticosteroids; fall of circulating eosinophils and lymphocytes; and elevation of polymorphonuclear neutrophils.

**B For clinical effects, uses, and dosages,** see p 583.

#### Pituitary Growth Hormone (PGH)

"Pure" PGH has been employed in normal humans, pituitary dwarfs, and panhypopituitary individuals. Only the material prepared from human and possibly monkey pituitary glands has metabolic and growth promoting effect on humans. Because the amount of these materials produced is very small, they are available for experimental purposes only. The older crude growth hormone preparations have likewise been of no benefit under controlled experimental conditions.

#### Lactogenic (Luteotropic) Hormone.

This hormone has not been employed extensively in human research. Its presence is necessary for the initiation and apparently for the continuation of lactation in breasts which have been prepared for lactation by estrogen and progesterone during pregnancy.

#### Follicle-Stimulating Hormone (FSH)

FSH has different actions in male and female. In the female FSH stimulates the development of ovarian follicles. In the male it stimulates the germinal epithelium of the testis to produce spermatozoa. It apparently has no effect on the Leydig cells, hence does not influence testosterone secretion. Human pituitary FSH and FSH from the urine of menopausal women have been used in amenorrhea followed by chorionic gonadotropin to induce ovulation.

#### Interstitial Cell-Stimulating Hormone (ICSH) (Luteinizing Hormone).

In the female ICSH apparently has a dual action: it stimulates the growth of theca lutein cells and transforms the mature follicles into corpora lutea. In the male it stimulates the Leydig cells of the testis to secrete testosterone.

There is no good commercial pituitary ICSH. Chorionic gonadotropins, which have a similar action, are used clinically.

#### Thyroid Stimulating Hormone (TSH, Thyrotropin)

TSH is exceedingly efficient in stimulating the thyroid gland. It has limited clinical usefulness at present, its principal uses are to differentiate pituitary hypothyroidism from primary hypothyroidism or from low radioiodine uptake due to exogenous thyroid hormone or iodine. It has also been used in an attempt to "stimulate" metastatic thyroid cancer to take up radioiodine for therapeutic purposes.

Thyrotropin has been advocated for the treatment of thyroiditis, but its place in the

management of this disease is still open to question

The dosage is 5-10 units I M every 12 or 24 hours for 1-3 days. Repeat radioiodine uptake or PBI. If uptake or PBI is increased, primary hypothyroidism is not present

### POSTERIOR PITUITARY HORMONES

The posterior pituitary hormones are polypeptides composed of 8 amino acids. Their exact chemical structures have been determined and they have recently been synthesized. Like the anterior pituitary hormones they are effective only when administered parenterally (give I M), but they can also be absorbed through the nasal mucous membranes (as snuff). They exert 3 actions: They (1) raise BP (pressor action), (2) cause fluid retention without osmotically equivalent sodium retention (antidiuretic action), and (3) cause uterine contractions (oxytocic action).

To date the antidiuretic and pressor principles have not been fully separated; they may be identical. The oxytocic factor may likewise have some pressor effect.

#### Clinical Indications

**A Pressor-antidiuretic.** The pressor and antidiuretic principle is used primarily for the treatment of diabetes insipidus and to prevent and control abdominal distention. (For Diabetes Insipidus see p 513.)

**B Oxytocin** is employed in obstetrics for induction of uterine contractions.

#### Preparations Available\*

Name	Action	Average Dose
Vasopressin tannate (Pitressin Tannate®)	Antidiuretic pressor	0.3-1 ml I M every 12-72 hours
Vasopressin injection (Pitressin®)		0.25-0.5 ml I M every 3-4 hours
Posterior pituitary powder (snuff)		5-20 mg 3-4 times daily
Oxytocin injection (Pitocin®), synthetic oxytocin (Syntocinon®)	Oxytocic	0.3-1 ml I M as needed

\*Synthetic lysine vasopressin will soon be released as an aqueous nasal spray for the treatment of diabetes insipidus.

### PITUITARY-LIKE HORMONES ELABORATED BY THE PLACENTA

The most important of the pituitary-like hormones is that elaborated by the placenta during pregnancy. The hormone is referred to as "chorionic gonadotropin." Its physiologic action is almost identical with that of ICSH (see above). It has been shown that this hormone apparently functions only if an intact anterior pituitary gland is present. It is of little value by itself in inducing spermatogenesis or ovulation or maintaining a functional corpus luteum, but it may be effective for these purposes if preceded by pituitary FSH. Many of its alleged effects have been due to the presence of FSH, whose action the presence of chorionic gonadotropin may potentiate.

#### Clinical Indications.

In the male, chorionic gonadotropin may induce descent of cryptorchid testes in selected cases and is useful in some types of hypogonadism (although testosterone is generally preferred). In the female, chorionic gonadotropin may aid in inducing ovulation and maintaining corpus luteum in a few selected cases of sterility (if adequate FSH is present).

#### Preparations Available.

**A** Chorionic gonadotropin derived from the urine of pregnant women, is available commercially under a variety of trade names (e.g., APL®, Follutein®).

**B** Equine gonadotropins, derived from the serum of pregnant mares, are also available commercially. This preparation is a mixture of FSH and ICSH. It is not generally recommended because of its marked sensitizing effect and because antihormones are produced by protracted use. Only short courses should be employed.

#### Average Doses

The usual doses are 200-1000 units I M, every day or every other day.

### THYROID HORMONE

The active principles of the thyroid gland appear to be the iodine-containing amino acids thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ).  $T_3$  (sodium liothyronine, Cytomel®) is about 4 times as potent as  $T_4$  and acts more rapidly. Thyroid hormones act as a general cellular

metabolic stimulant with resultant increased oxygen consumption (i.e., increased metabolic rate). Their exact mode of action is not known.

#### Method of Administration.

Thyroid hormone, either in the form of thyroglobulin (desiccated thyroid),  $T_4$  or  $T_3$  is effective when taken orally. There is a marked difference in rates of metabolic responses between  $T_3$  and thyroid or  $T_4$ . In the case of  $T_4$ , little effect is noted after a single dose for about 24 hours, and the maximal effect is not reached for several days. After the medication is stopped there is a slow loss of the effect, depending upon the initial BMR and the level reached during thyroid medication. In general, at least 3-6 weeks must elapse after thyroid medication has been discontinued before one can be reasonably certain that the effects have been dissipated. In the case of  $T_3$ , the peak effect is reached in 12-24 hours and the effect is over in about 6-14 days or less.

The dextrorotatory isomers of  $T_4$  and  $T_3$  have recently become available. They exert a less marked "metabolic" effect in the same dosages in which  $T_4$  and  $T_3$  are given. They have been advocated primarily as cholesterol-lowering agents. Other analogues - in which such compounds as propionic or acetic acid are substituted for the alanine side chain or in which fewer iodine atoms are incorporated into the molecule - have also been studied.

#### Clinical Indications.

Thyroid hormone is indicated only in thyroid deficiency states. It is not effective and not indicated as a general metabolic stimulant. It has been shown that patients with thyroid deficiencies rarely require over 0.2 Gm (3 gr) of desiccated thyroid daily. Patients without deficiency states can easily tolerate 0.3-0.5 Gm (5-7 1/2 gr) or more daily without any effect on BMR, although the radioiodine uptake is suppressed. A good general rule is that if a patient requires over 2-3 gr of thyroid daily, his need for thyroid medication should be questioned.

#### Preparations & Dosages.

**A Desiccated Thyroid.** This is an excellent compound for thyroid replacement. There is no evidence that any of the commercial preparations which contain more or less iodine than the official preparation are any less "toxic." To avoid confusion in dosages, always use a standardized official thyroid. The dose is 65-200 mg (1-3 gr) daily.

**B L-Thyroxine Sodium ( $T_4$ ).** The principal advantage of this compound over desiccated thyroid is its assured constant potency. Because it is about 600 times as potent as thyroid, small changes in dose may lead to toxic levels. 0.1 mg is equivalent to 100 mg (1 1/2 gr) of desiccated thyroid.

**C Sodium Liothyronine ( $T_3$ , Cytomel<sup>®</sup>).** This preparation has a more rapid action and disappearance of effect than thyroid or thyroxine, and is 3-4 times as calorogenic as  $T_4$ . The average maintenance dose is 0.05-0.1 mg daily.

### PARATHYROID HORMONE

Parathyroid hormone is a protein substance derived from parathyroid glands. It is only effective when given parenterally.

Parathyroid hormone has a major effect on calcium and phosphorus and hence bone metabolism. Its effect is to cause an increased renal excretion of phosphorus and a direct decalcification of bone through stimulation of the osteoclasts, leading to mobilization of calcium and phosphorus from bone.

Because of the high cost and general unavailability of parathyroid hormone, 2 other preparations are employed in its place. They are dihydrotachysterol (AT 10) and vitamin D. Both of these are steroids and are effective by mouth. Although at first AT 10 was the preparation of choice, it now appears that vitamin D, which is less expensive, is almost equally effective.

#### Clinical Indications.

Parathyroid hormone is indicated only in acute postsurgical hypoparathyroid tetany (after accidental removal of the parathyroid glands) and for special tests (see Ellsworth-Howard test).

#### Preparations Available for Treatment of Hypoparathyroidism

**A Parathyroid Injection.** The average dose is 50-100 units (0.5-1 ml) in aqueous solution 3-5 times daily I.M. as indicated.

**B Dihydrotachysterol (Hytakerol<sup>®</sup>).** For dosage see Hypoparathyroidism.

**C Calciferol (Vitamin D<sub>2</sub>).** This preparation has a potency of 40,000 units/mg. The dosage is 1-5 mg (1/60-1/12 gr) daily.

## ADRENOCORTICAL HORMONE

The hormones of the adrenal cortex are all steroids. To date over 30 different steroids have been isolated and identified from animal adrenal glands or adrenal venous blood. Only a few of these have demonstrable metabolic effects.

The question has been raised whether all the steroids apparently isolated from the adrenal cortex are in fact naturally occurring or whether they are artifacts products in the chemical laboratory. Isolation of hormones from blood obtained by catheterization of renal veins shows that about 90% of the hormones of the adrenal cortex are 11-17 hydroxycorticosterone (compound F) and about 10% corticosterone (compound B). In general it may be stated that the best demonstration of the effects of adrenocortical hormones or hormones is that seen following corticotropin (ACTH) administration (see p. 583).

Aldosterone has been isolated from adrenals. This hormone appears to have only sodium and water retaining and potassium losing effects. It is about 20 times as potent as desoxycorticosterone.

Hormones with estrogenic and androgenic effects have also been isolated.

### Clinical Indications

**A Desoxycorticosterone Acetate (DOCA®)**  
The only significant metabolic effects of this hormone are sodium and water retention and increased urinary potassium excretion. In this respect it is about 20 times as potent as cortisone. It has little effect on carbohydrate or protein metabolism.

**B Cortisone Acetate** The principal metabolic effects of cortisone include retention of some sodium and water, increased excretion of nitrogen, potassium and phosphorus, increased blood glucose and ability to maintain blood glucose levels during fasting in Addisonian patients and return of the EEG pattern to normal in Addisonian patients. One of the most important effects is the adrenocortical atrophy which results with prolonged use. This is probably due to endogenous ACTH inhibition and may interfere with the normal response of the pituitary-adrenal axis to stress.

For clinical effects and use see p. 583.

**C Hydrocortisone** This compound is available for oral, I.V. and local (e.g. intra-articular) use. Its actions are similar to those of cortisone and its metabolic effects appear to be identical. It is somewhat more potent

than cortisone on a weight basis. Hydrocortisone phosphate (Hydrocortone® Phosphate) and hydrocortisone sodium succinate (Solu Cortef®) are also available for I.V. or I.M. use.

**D Cortisone and Hydrocortisone Analogues** Many modifications have been made in the cortisone-hydrocortisone molecule to decrease side reactions in relationship to therapeutic effect. The only beneficial effects of these modifications have been to decrease the sodium retaining and potassium losing effects of the compounds. All of these preparations are more potent on a weight basis than their parent compounds. The most important drugs in this group are as follows:

1 Prednisone and prednisolone are about 3-5 times as potent as cortisone and hydrocortisone, respectively.

2 Derivatives of prednisolone (There is no indication that any of these preparations offer any advantage over prednisolone itself.)

(1) Methylprednisolone (Medrol®) is about 10-20% more potent than prednisolone.

(2) Triamcinolone (Aristocort® Kenacort®) is about as potent as methylprednisolone.

(3) Dexamethasone (Deronil® Decadron® Hexedrol® Gamma Corten®) is about 7 times as potent as prednisolone. It may have slightly greater sodium retaining and potassium losing properties.

(4) Betamethasone (Celestone®) is similar in action and potency to dexamethasone.

(5) Paramethasone acetate (Haldrone®) is about 2-5 times as potent as prednisolone.

(6) Fluprednisolone (Alphadrol®) is about 2-5 times as potent as prednisolone.

**E Fluorocortisone acetate (Alflorone® Florinef® F Cortef®) and fludroprednisolone** are potent anti-inflammatory drugs which have been found useful in Addison's disease and also in dermatologic disorders. They have powerful sodium retaining effects. Except in Addison's disease they must be used locally only and even with local use their absorption may cause excessive sodium retention.

**F Whole Cortical Extract** A water-soluble extract of the adrenal gland. Although its steroid content (if any) and mode of action are poorly understood, this agent appears to be of value only for an occasional patient who fails to respond to cortisone in the emergency management of adrenal crisis.

### Preparations Available

**A Desoxycorticosterone Acetate (DOCA®) or Desoxycorticosterone Trimethylacetate**

Used only for supplementary maintenance in Addison's disease

1 Buccal tablets - DOCA<sup>®</sup> is ineffective when swallowed. The dosage is 1/2-2 tablets daily dissolved in the buccal gutter. The drug is almost equally effective in a given dose as when injected.

2 Solution in sesame oil - The dosage is 1-3 mg I M daily for maintenance.

3 Pellets - The dosage is one 75 mg pellet for each mg of DOCA<sup>®</sup> required by injection, up to 3 mg/day. If requirements by injection exceed 3 mg, one additional pellet should be implanted (e.g., for a requirement of 5 mg/day by injection, implant 6 pellets). The duration of action is 6-8 months.

4 Desoxycorticosterone trimethylacetate (the most practical preparation), 25-75 mg I M once a month.

B Adrenal Cortex Extract (Rarely used) May be administered I M, subcut or I V in treatment of Addisonian crisis. The dosage is 10-100 ml or more daily as indicated.

C Lipo-Adrenal Cortex Sterile Solution (Rarely used) Administered I M only. The dosage is 5 ml I M daily during crisis in addition to aqueous adrenal cortical extract, 1-2 ml daily for maintenance.

D, Cortisone (Compound E) See p 586

E Hydrocortisone (Compound F) See p 586

F Fluorocortisone See p 588

G Prednisone and Prednisolone See p 586

H Aldosterone Antagonist Spironolactone (Aldactone<sup>®</sup>, 100 mg or Aldactone A<sup>®</sup> 25 mg oral tablets), for states of excessive aldosterone production and edema.

## ADRENAL MEDULLARY HORMONES

The adrenal medulla contains 2 closely related hormones: epinephrine (about 80%) and norepinephrine (about 20%). The 2 have different actions, as outlined below.

Since epinephrine may be synthetic or derived from natural sources (usually the latter) and thus contaminated with norepinephrine, the reason for some of the apparently paradoxical physiologic effects of the present preparation becomes clearer.

Substance	Blood Vessels	Cardiac Output	BP	Blood Glucose
Epinephrine	Vasodilation (over-all) usually	Increased	Elevated ?	Elevated
Norepinephrine (Levarterenol)	Vasoconstriction (over-all)*	No effect	Elevated	Elevated 1/8 that of epinephrine

\*Vasodilator of coronary arteries

Epinephrine causes an immediate elevation of blood glucose by inducing glycogenolysis in liver and muscle.

### Epinephrine

A Clinical Uses Epinephrine is used in a great many clinical conditions including the following: Allergic conditions (e.g. bronchial asthma, urticaria, angioneurotic edema) for control of superficial bleeding especially from mucous membranes with local anesthetics to slow down absorption rarely in cardiovascular disorders (e.g. Stokes Adams syndrome, cardiac arrest) and in tests of hepatic glycogen storage.

### B Preparations Available

1 Epinephrine Injection is usually administered subcut but may be given I M and even I V if diluted in 1 L of solution. The dosage is 0.2-1 ml of 1:1000 solution as indicated.

2 Epinephrine Inhalation 1:100 for inhalation only.

3 Epinephrine in oil injection 1:500 administered only I M. The usual dose is 0.2-1 ml.

### Levarterenol (Norepinephrine)

A Clinical Indications Levarterenol is used almost exclusively for its vasopressor effect in acute hypotensive states (surgical and nonsurgical shock, central vasomotor depression and hemorrhage, see p 4) and in the preoperative management of pheochromocytoma.

B Preparations Available Levarterenol bitartrate (Levophed<sup>®</sup>) 0.2% solution containing 1 mg free base/ml (1:1000) in ampules containing 4 ml.

C Mode of Administration Add 4-16 ml of levarterenol (or occasionally more) to 1 L of any isotonic solution and give I V through a Murphy drip bulb. Determine response and then maintain flow at a rate calculated to main-

tain BP (usual rate 0.5 l ml/min). Note: Levarterenol is a very potent drug and great care must be employed in its use. Do not allow the solution to infiltrate the tissues or slough may result.

**D Levarterenol Antagonist** Give phen tolamine (Regitine®) 5 mg I V for the pre operative diagnosis of pheochromocytoma and larger amounts I M or orally for the operative management of pheochromocytoma.

### MALE SEX HORMONE (Testosterone)

Of the many steroid hormones which have been isolated from the testis, the most potent androgen is testosterone. It is believed therefore that testosterone is the male sex hormone. Testosterone is responsible for the development of secondary sex characteristics in the male (i.e. facial hair, deep voice, development of penis, prostate and seminal vesicles). Administration of testosterone to the female causes development of male secondary sex characteristics. In the female, the adverse androgenic effects can only be partially overcome by the simultaneous administration of estrogens.

Perhaps of greater importance than its androgenic effect is the protein anabolic (tissue building) effect of testosterone. Testosterone also has mild sodium chloride and water retaining effects. It should be used with caution in children to prevent premature closure of the epiphyses.

Free testosterone and testosterone propionate are not effective when swallowed. The only way to administer these agents effectively is parenterally by I M injection or as implanted pellets. Testosterone preparations which do not occur naturally (e.g. methyltestosterone (MT)) are effective when swallowed. Methyltestosterone in humans induces a marked creatinuria and has apparently produced jaundice after prolonged administration; otherwise, however, its metabolic and androgenic effects are similar to those of testosterone and testosterone propionate. Testosterone and testosterone propionate, when injected, are partially (about 30-50%) excreted as 17 keto steroids in the urine. Methyltestosterone is not excreted as 17 keto steroid; in fact, its administration will result in diminished urinary 17 keto steroids due to diminished endogenous testosterone production.

### Clinical Indications

In either sex, testosterone may be indicated in any debilitating disease for its protein anabolic function. In addition, there are certain uses specific to each sex.

**A Males** Testosterone is used as replacement therapy in failure of endogenous testosterone secretion (e.g. eunuchoidism, male climacteric). Its use in impotence, angina pectoris, homosexuality, gynecomastric and benign prostatic hypertrophy is without benefit.

**B Females** Testosterone is used in women for functional uterine bleeding, endometriosis, dysmenorrhea, premenstrual tension, advanced breast carcinoma, chronic cystic mastitis, and suppression of lactation. The virilizing effects limit the total amount that can be used. While 150-300 mg of testosterone per month are said to be a safe dose, smaller doses may virilize a susceptible patient.

### Preparations & Dosages

**A Testosterone (Free)** The most common method of administration is in aqueous solution 1 M. The dosage is similar to that of testosterone propionate in oil (below). Pellets may be implanted subcut. The dosage is 4-8 pellets (containing 75 mg each) over 3-4 months.

**B Testosterone Propionate in Oil** The dosage is 10-100 mg I M every 2-3 days.

**C Testosterone Cyclopentylpropionate in Oil (Depo Testosterone®)** The duration of action is 2-5 times or more than that of testosterone propionate. The dosage is 100-200 mg weekly to 500 mg monthly in a single dose.

**D Testosterone Enanthate in Oil (Delta Testryl®)** The duration of action is comparable to that of testosterone cyclopentylpropionate. The average dose is 200-400 mg I M every 3-4 weeks.

**E Methyltestosterone** The dosage is 5-25 mg daily. Note: Do not use methyltestosterone in the treatment of thyrotoxicosis, acromegaly and gigantism, or liver disease.

**F Fluoxymesterone (Halotestin® Ora Testryl® Uldandren®)** This drug is a fluoro derivative of methyltestosterone. It is about 2-5 times as potent as the parent drug. Its toxicity is similar to that of methyltestosterone.



## ESTROGENS

It has less effect than other preparations on epiphyseal closure and is therefore the drug of first choice in children, but it must be used cautiously. The dosage is 2-10 mg. orally daily.

G. Stanozolone (Neodrol®). The dosage is 50-150 mg. once or twice a week.

H. Anabolic Hormones: Several new drugs have been introduced whose relative protein anabolic effects (vs. their androgenic effects) are claimed to be greater than those of the other testosterone preparations listed above. Most of them appear to induce BSP retention, and they may have other as yet unrecognized side effects. Norethandrolone (Nilevar®) is given in dosages of 30-50 mg. daily orally (see p. 582).

I. Methandrostenolone (Dianabol®). This drug has a definite androgenic effect in some women at doses of 10-15 mg./day, and may cause BSP retention by the liver after prolonged use. The average dose is 5 mg./day.

J. Nandrolone phenylpropionate (Durabolin®). The dosage is 25 mg./week or 50-100 mg. every 2 weeks I.M. or subcut. Skin reactions may occur in some patients.

K. Oxymetholone (Anadrol, Androyd®). The dosage is 2.5 mg. orally t i d.

#### Choice of Preparations.

In view of the great number of preparations available, it may be difficult to decide which one to use. The physician should choose those preparations which are most economical to the patient and still are effective. The use of short-acting testosterone preparations by repeated injections should be reserved only for those very few conditions in which the patient must be under close observation (preferably in a hospital) or when the dose must be very exact (i.e., research). The preparations of choice when both androgenic and anabolic effects are desired are either methyltestosterone orally or one of the longer-acting testosterone I.M. or subcut. If less androgenicity is desirable one of the newer anabolic agents should be considered, although much more experience will be needed before their true effectiveness has been determined.

Caution: Men receiving testosterone should be observed carefully for prostatic cancer. The virilizing effect of testosterone in women may become permanent even after withdrawal of testosterone.

Estrogens control proliferation of endometrium, changes in vaginal cells (cornification and lowering of vaginal pH below 4.0), and ductal proliferation of breasts. They stimulate osteoblastic activity and have a slight protein anabolic effect and a moderate sodium- and water-retaining effect. They may also have a cholesterol-lowering effect.

#### Clinical Indications

Estrogens are useful in both men and women for their effect on osteoblasts in the treatment of osteoporosis. In women, estrogen is used as replacement therapy in cases of ovarian failure (e.g., menopause). In men, it is used as an adjunct in the treatment of carcinoma of the prostate.

#### Preparations & Dosages.

Many substances have estrogenic activity, including some nonsteroids (e.g., diethylstilbestrol, dienestrol, hexestrol). However, only some of the steroids are useful clinically. There is no evidence that any of the estrogens are less "toxic" than others. Toxicity (e.g., nausea and vomiting) is usually due to overdosage. Most of the estrogens exert profound physiologic effects in very small doses, and their therapeutic and toxic dosage are quite similar. The physician should familiarize himself with the use of one or two preparations and resist the tendency to try out new ones.

There is little need at present to administer estrogens by any but the oral route, absorption in the gastrointestinal tract seems to be complete, and there is no evidence that nausea and vomiting can be minimized by parenteral administration. There is likewise no evidence that the "naturally-occurring" estrogens are any more effective than the synthetic ones, although they may be better tolerated.

Although estrogens apparently play a role in mammary tumors of animals, there is no evidence that they are carcinogenic in humans. Even so, it is advisable to perform periodic breast examinations and Papanicolaou smears in patients receiving prolonged estrogen therapy. Cyclic administration is always preferable when estrogens must be given over long periods.

#### A. Nonsteroid Estrogens:

1. Diethylstilbestrol - A synthetic nonsteroid estrogen, an excellent preparation, and the cheapest available. The dosage is 0.5-1 mg. daily orally.

2. Hexestrol, dienestrol, benzenestrol, chlorotrianisene (TACE®), methallenestrol

(Vallestril<sup>®</sup>) These preparations have no advantage over diethylstilbestrol and are more expensive. The dosage is 0.2-0.5 mg daily orally.

#### B Steroidal Estrogens for Oral Use

1 Ethinyl estradiol. An excellent synthetic estrogen. The dosage is 0.02-0.05 mg daily orally.

2 Conjugated estrogenic substances (estron sulfate) (e.g. Premarin<sup>®</sup>, Amnestrogen<sup>®</sup>). A natural estrogen which is well tolerated. The dosage is 0.6-2.5 mg daily orally.

#### C Estrogens for Injection

1 Estrone (Theelin<sup>®</sup>). Little used at present; the conjugated estrogens listed above are preferred. The dosage is 1 mg 2-3 times weekly or 1000 units daily I.M.

2 Estradiol valerate in sesame oil (Del estrogen<sup>®</sup>). A long acting estrogen. The dosage is 10-20 mg I.M. every 2-3 weeks.

3 Estradiol benzoate injection in oil. The dosage is 0.5-1 mg every other day I.M.

4 Estradiol dipropionate injection. This preparation has a slightly longer duration of effect than estradiol benzoate. The dosage is 2.5 mg I.M. 1-2 times weekly.

5 Conjugated estrogenic substances (estron sulfate) 2.5 mg daily I.M. Premarin<sup>®</sup> I.V. (20 mg) is a rapid acting preparation which is given to stop bleeding in menorrhagia.

### PROGESTINS (Gestagens)

Up to the present time progesterone has had a limited use in clinical medicine. Recently a number of new compounds with progesta-

tional activity have been introduced. However, these new compounds also have other reactions which are summarized below.

Progesterone leads to the secretory phase of endometrium. In the absence of estrogens it does not have any significant effect on the uterus; i.e. the uterus must be stimulated (proliferated) by estrogens before progesterone can act. Progesterone also causes acinar proliferation of breasts.

#### Clinical Indications

A Progesterone may be used with estrogens to maintain more normal cyclic menstrual function in women who otherwise do not menstruate.

B Medical D and C Progesterone is used to produce the so called medical dilatation and curettage which is actually a test of adequacy of endogenous estrogen production. If withdrawal bleeding does not occur it may also indicate that the patient is pregnant. The test may be performed in one of 3 ways:

1 Give 10 mg of progesterone I.M. daily for 5 days. If menstrual bleeding occurs within 2-5 days after stopping endogenous estrogen production is adequate.

2 Give 20 mg of norethindrone (Norlutin<sup>®</sup>) or medroxyprogesterone (Provera<sup>®</sup>) orally daily for 4-5 days. If menstrual bleeding occurs within 2-3 days endogenous estrogen production is adequate.

3 Give 250-375 mg of hydroxyprogesterone caproate (Delalutin<sup>®</sup>) I.M. once. If menstrual bleeding occurs within 10-16 days endogenous estrogen production is adequate.

C Obstetric Use. The progestins are used in large doses in some cases of habitual or threatened abortion, e.g. hydroxyprogesterone caproate (Delalutin<sup>®</sup>) 500 mg I.M. / week.

Hormones With Progestational & Other Activity\*

	Progestational	Androgenic	Estrogenic	Contraceptive	Dosage
Norethandrone (Norlutin <sup>®</sup> )	4+	0	2+	4+	20-50 mg daily orally
Norethindrone acetate	4+	0	2+	4+	10-20 mg daily orally
Norethandrolone (Nilevar <sup>®</sup> )	3+	2+	0	3+	30-50 mg daily orally
Norethynodrel and ethinyl estradiol (Enovid <sup>®</sup> )	4+	0	4+	4+	5-30 mg daily orally

\*Modified from Buckner and Herrmann. Yale J Biol & Med 30:446, 1958.

**D. Use as Contraceptive:** Some of the newer agents are being used effectively as contraceptives, they act by preventing ovulation. Enovid® (norethynodrel and ethinyl estradiol) has been most widely studied for this purpose. Give 5-10 mg. daily beginning on the fifth day after onset of menses and continue for 20 days, then resume on the fifth day of the cycle, etc.

**E. In endometriosis** the progestins, at times combined with estrogens, are used continuously in large dosage to induce a state of pseudopregnancy.

#### Preparations & Dosages.

##### A. True Progestational Hormones

1. Progesterone, 5-10 mg daily I.M., or 100-200 mg. daily orally or I.M. (for threatened or habitual abortion)

2. Hydroxyprogesterone caproate (Delalutin®), 125-250 mg I.M. every 2 weeks

3. Ethisterone, 60-100 mg daily orally

4. Medroxyprogesterone (Provera®), 10-30 mg./day orally, or 100 mg I.M. every 2 weeks (for endometriosis only).

**B. Hormones With Progestational (and Other) Activity:** See table on p 583.

#### Side Effects of Progesterone Treatment.

Prolonged progesterone therapy may cause abdominal distention, nausea, acne, masculinization of a female fetus, and decidua casts ("pseudomalignant changes") of the endometrium.

#### Symposium (A. E. Rakoff, consulting editor):

New steroid compounds with progestational activity. Ann. New York Acad. Sc. 71:479-806, 1958.

#### MISCELLANEOUS OVARIAN HORMONES

Various other hormones of the ovary have been described. Two which have a relaxant effect on the uterus have been prepared for clinical use. They may be identical. The exact place of these drugs in clinical therapy has not yet been established.

#### Relaxin (Relasin®, Cervilaxin®).

For premature labor or threatened abortion. Dosage varies with indications.

#### Lututrin (Lutrexin®).

Possibly useful in dysmenorrhea, threatened abortion, and premature labor. Dosage varies with indications.

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#### CLINICAL USE OF CORTICOTROPIN (ACTH) & THE CORTISONES

Both pituitary adrenocorticotropin (ACTH), acting by adrenal stimulation, and the C-11-oxygenated adrenal steroids (cortisone) have been shown to have profound modifying effects on many disease processes. These effects cannot be explained at present on the basis of the known metabolic and immunologic activities of these compounds (see p 575).

These agents do not appear to "cure". Their action appears to be a modification of cellular activity or permeability so that "toxins" no longer can affect the cell. When the drug is discontinued the disease may rapidly recur.

No other hormones or combinations of agents that are available commercially today have the same effects as these substances.

In general these agents are interchangeable, but occasionally a patient will be responsive to one and not to another.

#### Toxicity & Side Reactions.

These agents are potentially very dangerous, but with proper precautions most of these dangers can be avoided.

**A. Hyperglycemia and glycosuria** (diabetogenic effect) is of major significance in the early or potential diabetic.

**B. Marked retention of sodium and water**, with subsequent edema, increased blood volume, and hypertension is minimized by the use of the newer agents.

**C. Negative nitrogen balance** may occur, with loss of body (including bone) protein and consequent osteoporosis.

**D. Potassium loss** may lead to hypokalemic alkalosis.

**E. Hirsutism and acne** are especially disagreeable in females. Amenorrhea may occur.

F Cushing's features or facies may develop with prolonged administration

G. Peptic ulcer may be produced or aggravated

H Resistance to infectious agents is lowered

#### Controls to Be Employed to Correct or Minimize Dangers

A Always reduce the dosage as soon as consistent with the clinical response

B During the first 2 weeks of therapy BP and weight should be carefully observed. Take an initial CBC and sedimentation rate and repeat as indicated. Determine the urine glucose, if reducing substances are found in the urine, determine fasting blood glucose. Serum potassium,  $\text{CO}_2$ , and chloride should be checked occasionally if large doses of these hormones are to be given over a period of more than several days. Eosinophil count or measurement of urinary steroid excretion is indicated if any question of lack of adrenal response to corticotropin arises

C All patients should be on high-protein diets (100 Gm or more of protein daily)

D If edema develops, place the patient on a low-sodium diet (200-400 mg of sodium daily). Diuretics (see p. 236) may be employed when strict sodium restriction is impossible

E Potassium chloride as enteric-coated tablets or in solution, 3-15 Gm daily in divided doses, should be administered if prolonged use or high dosage is employed

F In cases of long-continued administration, testosterone preparations (see p. 580) may be used to counteract the negative protein and potassium balance

G Do not stop either drug abruptly since sudden withdrawal may cause a severe "rebound" of the disease process. Also remember that cortisone (or hydrocortisone) causes atrophy of the adrenal cortex, probably through endogenous ACTH inhibition; sudden withdrawal may lead to symptoms of Addison's disease

H. When treating mild disorders, give steroids during the daytime only since this causes less suppression of endogenous ACTH.

When discontinuing therapy, withdraw the evening dose first

#### Contraindications & Special Precautions.

A. Stress in Patients Receiving Maintenance Corticoids: Patients receiving corticoids, especially the oral preparation (or even ACTH) must be carefully watched because suppression of endogenous ACTH interferes with the normal response to stressful situations (e.g., surgery or infections). Patients should be warned of this danger, and probably should carry identification cards showing what drug they are taking, the dosage, and the reason for taking it. Whenever such a situation occurs or is about to occur, the dosage of cortisone or hydrocortisone should be increased or parenteral corticoids given (or both). If oral cortisone or hydrocortisone can be administered, it must be administered in larger doses at least every 6 hours.

B Heart Disease: These agents should be used with caution in patients with a damaged myocardium. The increase in extracellular fluid may lead to cardiac decompensation. Always begin with small doses and place the patient on a low-sodium diet.

C Severe Renal Disease: With the exception of nephrosis, these drugs are probably contraindicated or should be used with extreme caution in patients with major renal damage associated with edema or oliguria

D Predisposition to Psychosis: These drugs cause a sense of well-being and euphoria in most persons, but in patients who are predisposed to psychosis an acute psychotic reaction may occur (insomnia may be the presenting symptom in impending psychosis.) In these cases the drug should be stopped or the dosage reduced, and the patient should be carefully observed and protected. Persons have committed suicide under the influence of these drugs

E Effect on Thyroid: When given for prolonged periods, these drugs may depress thyroid function

F Effect on Peptic Ulcer: Active peptic ulcer is a contraindication to the use of these drugs because of the danger of perforation or hemorrhage. These agents also tend to activate ulcers, and should be used only in emergency situations or with optimal anti-ulcer therapy in patients who have a history of peptic ulcer.

G. Tuberculosis: Active or recently healed tuberculosis is a contraindication to the use of these drugs unless intensive antituberculosis therapy is also carried out. A chest x-ray should be taken before and periodically during treatment with corticosteroids.

H. Infectious Diseases: Because these drugs tend to lower resistance and therefore to promote dissemination of infections, they must be used with extreme caution, even when appropriate antibiotics are being given, in any acute or chronic infection.

I. Diagnostic Errors: Administration of these drugs may interfere with certain immune mechanisms which are of diagnostic value, e.g., in skin tests and agglutination tests, they produce leukocytosis and lymphopenia, which may be confusing. The signs and symptoms of infection may be masked by corticosteroid therapy. These drugs may also interfere with normal pain perception (e.g., joint pain), which may lead to Charcot-like disintegration of the weight-bearing joints after local or systemic corticosteroid therapy.

J. A bleeding tendency has been reported as a side reaction in patients receiving the newer substituted hormones.

K. Thrombosis may occur, especially on sudden withdrawal or too rapid reduction of dosage.

L. Ocular Contraindications. These agents apparently stimulate the activity of herpes simplex virus and so are contraindicated for local use in herpes simplex keratitis. Local use in the eye is often complicated by fungal infections of the cornea. Cataract formation has been reported in patients with rheumatoid disorders who are receiving corticoids.

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Mills, L.C., & J.H. Moyer (editors): Inflammation and diseases of connective tissue. A Hahnemann symposium. Saunders, 1961.

Paris, J.; Pituitary-adrenal suppression after protracted administration of adrenal cortical hormones. *Proc. Staff Meet. Mayo Clin* 36: 305-17, 1961.

Reifenstein, E.C., Jr.; Control of corticoid-induced depletion and osteoporosis by anabolic steroid therapy. *Metabolism* 7:78-88, 1958.

## Corticotropin (ACTH) &amp; the Corticosteroids

Preparation	Daily Dosage	Remarks
<b>CORTICOTROPIN (ACTH)</b>		
Lyophilized powder	5 200 U	I V Administer in any I V fluid by slow drip For greater effect give I V during entire 24 hour period May use also for 8 12 hours Maximal effect obtained by I V use of 15 40 U
Solution	5 200 U	Subcut or I M Administer in saline every 6 hours By this route long acting preparations are usually used (see below) Give 40 200 U
Repository Injection (gel)	10 200 U	I M or subcut Longer acting than the powder or solution For maximum effect give every 12 hours May be used once daily in some patients
Corticotropin Zinc®	10 100 U	I M or subcut Duration of action 24 hours

## ORAL CORTICOSTEROIDS

Cortisone acetate	25 200 mg or more	For maximum effect use every 6 hours or q 1 d Rarely used clinically now (sodium retention and potassium excretion) except in Addison's disease
Hydrocortisone	20 200 mg or more	As for cortisone above About 1 5 times as potent as cortisone
Prednisone and prednisolone	5 50 mg or more (avg 10 20)	Δ 1 Derivative of cortisone and hydrocortisone Drug of choice has no significant sodium retaining effect About 4 times as potent anti inflammatory effect as parent drugs Give every 6 hours or q 1 d Good economical drug
Methylprednisolone (Medrol®)	4 40 mg (avg 8 16)	About 15 25% more potent than prednisolone No other apparent advantages
Triamcinolone (Aristocort® Kencort®)	4 40 mg (avg 8 16)	About the same as methylprednisolone May produce bizarre effects e g nausea weight loss dizziness and vague toxic symptoms
Dexamethasone (Decadron® Deronil®)	0 75 10 mg (avg 1 5 3)	0 75 dexamethasone 5 mg prednisolone May cause sodium retention especially at higher levels No reduction of other side reactions No advantages over prednisolone
Betamethasone (Celestone®)	0 6 6 mg (avg 1 2 2 4)	0 6 mg betamethasone 5 mg prednisolone No advantage over prednisolone
Paramethasone (Haldron®)	2 20 mg (avg 4 8)	2 mg paramethasone 5 mg prednisolone No advantage over prednisolone
Fluprednisolone (Alphadrol®)	1 5 15 mg (avg 3 6)	1 5 mg fluprednisolone 5 mg prednisolone No advantage over prednisolone
Fludrocortisone (Florine®)	0 1 0 3 mg	Used almost entirely in Addison's disease Potent sodium retaining effect (20 times that of hydrocortisone) Supplements hydrocortisone in Addison's disease May be useful also as diagnostic tool in adrenal hyperplasia

## PARENTERAL CORTICOSTEROIDS (1) For I V use only

Hydrocortisone I V infusion concentrate	100 200 mg	Most reliable emergency drug in absolute or relative adrenal failure CAUTION Must dissolve in at least 500 ml solution
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## PARENTERAL CORTICOSTEROIDS (2) For I V or I M use (Highly soluble Rapid action and rapid excretion)

Hydrocortisone sodium succinate (Solu Cortef®)	100 200 mg	Dissolve 1 10 ml or more of solution May administer in small volume or I V fluids Water soluble For emergency use Active I V or I M I M must be given every 6 hours for maximum effect
Prednisolone hemisuccinate (Metacortelone®)	50 100 mg	As for hydrocortisone sodium succinate above but not used in adrenal insufficiency Indicated when corticosteroids can not be taken orally

## Corticotropin (ACTH) &amp; the Corticosteroids (Cont d.)

Preparation	Daily Dosage	Remarks
<b>PARENTERAL CORTICOSTEROIDS (2) (Cont d)</b>		
Dexamethasone-21 phosphate (Decadron® phosphate injection)	3 40 mg	As for prednisolone phosphate, above
Prednisolone 21-phosphate (Hydeltrasol®)	40 100 mg	As for prednisolone hemisuccinate above
Methylprednisolone sodium succinate (Solu-Medrol®)	40 120 mg	As for prednisolone hemisuccinate above Also advocated as retention enemas in ulcerative colitis

**PARENTERAL CORTICOSTEROIDS (3) For I M Systemic use (Insoluble Slowly absorbed and excreted)**

Cortisone acetate aqueous suspension	25 200 mg	I M only in doses every 12 24 hours Used as long acting parenteral corticosteroid mainly in adrenal insufficiency
Methylprednisolone acetate	10 80 mg	As hydrocortisone May be used systemically for anti inflammatory effect (Dosage 40 180 mg in single dose)

**PARENTERAL CORTICOSTEROIDS (4) For local use only (intrasynovial soft tissues) Very insoluble Many preparations available (1) Hydrocortisone acetate 25 mg/ml (2) hydrocortisone tertiary butyl acetate (Hydrocortone® TBA) (5 ml vials 25 mg/ml) (3) prednisolone acetate aqueous suspension (Meticortelone®) (5 ml vials 25 mg/ml) (4) prednisolone tertiary butyl acetate (Hydeltra® TBA) (5 ml vials 20 mg/ml)****LOCAL CORTICOSTEROIDS** Almost all of the above steroids plus others [e.g. flurandrenolone (Cordran®)] have been incorporated into various vehicles for local application to the skin eyes or mucous membranes They are effective anti inflammatory agents when so used At present there appears to be little to choose among them**Bibliography**

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# Nutritional & Metabolic Disorders

Milton J. Chatton & Sheldon Margen

## VITAMINS & VITAMIN DISORDERS

In illness there may be considerable variation in the body's requirements for vitamins, depending upon age, activity, diet, metabolic rate, and other factors affecting vitamin absorption, utilization, and excretion. Vitamin deficiencies are almost always multiple, although a particular symptom complex may predominate.

Vitamin deficiencies are principally of one of 2 categories: the water-soluble (B complex) vitamins or the fat-soluble vitamins.

Early signs of vitamin deficiency are usually nonspecific, vague, and mild and are easily misinterpreted or missed entirely.

The crude sources of vitamins are often more effective in therapy than the pure or synthetic preparations, as a rule, only during the more severe phases of deficiencies is it necessary to use "pure" vitamins. The use of a "pure" vitamin in the face of a true multiple vitamin deficiency may aggravate rather than alleviate the condition. The treatment of vitamin deficiencies consists of giving an adequate balanced, high-protein, high-vitamin diet with vitamin supplementation as indicated. In general, it is wise to use vitamins therapeutically in 5-10 times the amounts required for daily maintenance.

Large doses of some vitamins are toxic and may cause illness, particularly when continued for long periods.

### FAT-SOLUBLE VITAMINS

#### 1. VITAMIN A

Vitamin A is an alcohol of high molecular weight which is elaborated in the liver by the

conversion of beta-carotene in foods. It is necessary for normal function and structure of all epithelial cells and for the synthesis of visual purple in the retinal rods (hence for vision in dim light). It is present in leafy green and yellow fruits and vegetables, whole milk, butter, eggs, fish, or liver oil. The recommended daily allowances for adults are 5000 I.U. (or U.S.P. units), during pregnancy and lactation 6000-8000 I.U.

#### Avitaminosis A.

**A Clinical Findings.** Mild or early manifestations consist of dryness of the skin, night blindness, and follicular hyperkeratosis. Severe or late manifestations are xerophthalmia, atrophy and keratinization of the skin, and keratomalacia.

**B Tests for Deficiency.** Dark adaptation is impaired. A low serum value (below 20 mcg/100 ml) of vitamin A may be helpful. It is not diagnostic. A therapeutic test with 25,000-75,000 I.U. daily for 4 weeks may be helpful.

**C Treatment.** Give oleovitamin A, 15 thousand units once or twice daily. If an absorption defect is present, it may be necessary to administer bile salts with the vitamin A or to give the same dosage in oil. I.M. (50,000 units/ml in sesame oil). Skin lesions may require more treatment.

#### Hypervitaminosis A

This disorder is rare in adults. The minimal toxic adult dose is about 75,000 units daily for 6 months.

**A Clinical Findings.** Anorexia, loss of weight, hair loss, hyperostosis and periosteal elevation of bone, hepatomegaly, splenomegaly, anemia, and skin rash.

**B Tests of Excess.** Serum levels of vitamin A over 400 mcg/100 ml are found.

**C Treatment.** Withdraw the medicinal source.



## 2. VITAMIN D

The vitamins D are sterols formed in the skin by ultraviolet irradiation of plant sterol precursors. They increase calcium absorption from the intestine and urinary phosphorus excretion. They are present in fish livers, their precursors are widely distributed in plants. The daily allowances for adults are not known. For children and for women during pregnancy and lactation, 400 units are recommended.

### Avitaminosis D.

Avitaminosis D is usually due to inadequate dietary intake, lack of sunlight, or an absorption defect.

**A. Clinical Findings** Lack of vitamin D leads to osteomalacia in children (rickets). Some cases of adult osteomalacia appear to be associated with increased requirements of vitamin D.

**B. Tests for Deficiency** Serum calcium and phosphorus may be normal or decreased and serum alkaline phosphatase is generally increased.

**C. Treatment** See Osteomalacia

### Hypervitaminosis D

This disorder is usually caused by prolonged ingestion of 5-150 thousand units daily.

**A. Clinical Findings** The manifestations of hypercalcemia are present and may progress to renal damage and metastatic calcification.

**B. Tests of Excess** Serum calcium elevation (over 11.5 mg./100 ml.) occurs if large doses of vitamin D are taken. (Always consider other causes of hypercalcemia.)

**C. Treatment.** Withdraw the medicinal source. Complete recovery will occur if overtreatment is discontinued in time.

## 3. VITAMIN K

The vitamins K are chemical compounds which are necessary for prothrombin synthesis by the liver and so are important in the blood coagulation mechanism. They are widely distributed in green leaves of plants, egg

yolk, and soybeans. They are also synthesized by microorganisms in the intestines. The daily allowances are not known.

### Avitaminosis K.

Avitaminosis K results from liver disease which interferes with synthesis of prothrombin, inadequate bile supply with poor absorption, or ingestion of drugs which depress prothrombin synthesis (e.g., coumarins, salicylates).

**A. Clinical Findings** Bleeding

**B. Tests for Deficiency** Prolonged prothrombin time

**C. Treatment** See Liver Disease, Bishydroxycoumarin Poisoning, and Hemorrhagic Disease of the Newborn

### Hypervitaminosis K

Large doses of vitamin K to infants, particularly premature infants, may cause hemolytic anemia, hyperbilirubinemia, hepatomegaly, and even death.

## WATER-SOLUBLE VITAMINS. VITAMIN B COMPLEX

The members of the vitamin B complex are intimately associated in occurrence as well as in function. As a result of this close interrelationship, it is doubtful that a deficiency of a single B vitamin ever exists except under experimental conditions. Deficiency of a single member of the B complex would probably lead to impaired metabolism of the others. Hence, although certain clinical features may predominate in the absence of a single member of the complex, this does not mean that the deficiency can be entirely corrected by replacing that factor alone. Therefore, "specific therapy" always consists of providing adequate dietary or parenteral sources of all members of the B complex.

## 1. VITAMIN B<sub>1</sub> (Thiamine Hydrochloride)

Vitamin B<sub>1</sub> is the coenzyme for decarboxylation of alpha-keto acids (e.g., pyruvic and alpha-ketoglutaric acid). It is important, therefore, for normal carbohydrate oxidation

Dietary sources are liver, lean pork, kidney, and whole grain cereals. Steaming or exposure to moist heat reduces the thiamine content of foods. The daily dietary allowances are about 0.5 mg /1000 Calories (avg , 1.2-1.6 mg /day)

#### Avitaminosis B<sub>1</sub> (Beriberi).

Avitaminosis B<sub>1</sub> results from an inadequate intake due usually to idiosyncrasies of diet or excessive cooking or processing of foods. The increased need for vitamin B<sub>1</sub> during fever, high carbohydrate intake, or thyrotoxicosis may lead to a deficiency.

**A. Clinical Findings.** Mild or early manifestations consist of vague multiple complaints suggestive of neurasthenia and include anorexia, formation and muscle cramps, calf tenderness, paresthesias and hyperactivity followed later by hypoactivity of knee and ankle jerks.

Severe or late manifestations (beriberi) are anorexia, polyneuritis, serous effusions, subcutaneous edema, paralysis (particularly in the extremities), and cardiac insufficiency manifested by tachycardia, dyspnea, edema and normal or decreased circulation time, elevated venous pressure, and nonspecific ECG changes.

**B. Treatment.** Give thiamine hydrochloride, 20-50 mg (1/3-3/4 gr) orally, 1 V or 1 M daily in divided doses for 2 weeks and then 10 mg (1/6 gr) daily orally. An alternative is to give dried yeast tablets (brewer's yeast), 30 Gm (1 oz) t i d. A well-balanced diet of 2500-4500 Calories/day should be given when tolerated.

## 2. VITAMIN B<sub>2</sub> (Riboflavin)

Riboflavin serves as coenzyme for hydrogen transfer. It is present in milk and milk products, leafy green vegetables, and liver. The daily dietary allowances for adults are 1.4-1.6 mg, in pregnancy and lactation, 2-2.5 mg.

#### Avitaminosis B<sub>2</sub> (Ariboflavinosis).

The etiologic factors in ariboflavinosis are similar to those of thiamine deficiency, but inadequate intake of milk is important. The manifestations of deficiency usually occur along with those of thiamine and niacin deficiency, but may occur earlier.

**A. Clinical Findings.** Mild or early manifestations are oral pallor, superficial fissuring at the angles of the mouth, conjunctivitis and photophobia, lack of vigor, malaise, weakness, and weight loss. Severe or late manifestations consist of cheilosis (fissuring at the angles of the mouth), fissuring of the nares, magenta tongue, moderate edema, dysphagia, corneal vascularization and circumcorneal injection, and seborrheic dermatitis.

**B. Treatment.** Give riboflavin, 40-50 mg (2/3-3/4 gr) I V, I M, or orally daily until all symptoms have cleared. An alternative is to give dried yeast tablets (brewer's yeast), 30 Gm (1 oz) t i d. A well-balanced diet consisting of 2500-4500 Calories/day should be given when tolerated.

## 3. NICOTINIC ACID (Niacin) & NICOTINAMIDE (Niacinamide)

Niacin and niacinamide function in important enzyme systems concerned with reversible oxidation and reduction. They are present in liver, yeast, meat, whole-grain cereals, and peanuts. The daily allowances for adults are 10-16 mg, for adolescents, 12-19 mg. Niacin may be used therapeutically as a vasodilating agent for headaches, myalgias, neurologic disorders, and edema of the labyrinth (100 mg or more daily in divided doses). Niacinamide does not possess this vasodilating effect.

#### Pellagra.

The etiologic factors in deficiency of these components of the B complex are similar to those of thiamine deficiency. Niacin deficiency is the principal but not the only dietary defect in pellagra, low tryptophan content of some foods also plays a role.

**A. Clinical Findings.** Mild or early manifestations consist of multiple vague complaints, a reddened, roughened skin, and redness and hypertrophy of the papillae of the tongue. Severe or late manifestations are marked roughening of the skin when exposed to light and friction, diarrhea, abdominal distention, scarlet red tongue with atrophy of papillae, stomatitis, depression, mental dullness, rigidity, and peculiar sucking reactions.

**B. Treatment.** Give nicotinamide (niacinamide), 50-500 mg (3/4-7 1/2 gr.) I V..

I.M., or orally daily until symptoms subside. Nicotinic acid (niacin) is less often used because of its vasodilating effect; the dosage is similar. Give therapeutic doses of thiamine, riboflavin, and pyridoxine also. An alternative is to give dried yeast tablets (brewer's yeast), 30 Gm. (1 oz.) t.i.d.

A well-balanced diet consisting of 2500-4500 Calories/day and ample proteins should be given when tolerated. Dementia may require constant supervision.

#### Nicotinic Acid Poisoning.

Large oral doses of nicotinic acid may cause flushing and burning of the skin and dizziness, but are usually not harmful. After I.V. administration hypotension may be severe. Anaphylaxis occurs rarely.

### WATER-SOLUBLE VITAMINS: VITAMIN C (Ascorbic Acid)

Vitamin C is concerned with the formation and maintenance of intercellular supporting structures (dentine, cartilage, collagen, bone matrix). Its biochemical action is not known. Dietary sources include citrus fruits, tomatoes, paprika, bell peppers, and all leafy green vegetables. The ascorbic acid content of foods is markedly decreased by cooking, mincing, air contact, alkalis, and contact with copper utensils. The dietary allowances for adults are 70-75 mg. daily, during pregnancy and lactation, 100-150 mg.

Ascorbic acid has been used in the treatment of certain poisonings in doses of 0.5 Gm or more, but proof of its value is lacking. It is used in dosages up to 200 mg. daily orally to promote healing of wounds or ulcers or during recovery from protracted disease (e.g., tuberculosis).

#### Avitaminosis C (Scurvy).

Scurvy is usually due to inadequate intake of vitamin C, but may occur with increased metabolic needs.

A. Clinical Findings: Mild or early manifestations are edema and hemorrhage of the gingivae, porosity of dentine, and hyperkera-

totic hair follicles. Severe or late manifestations consist of severe muscle changes, swelling of the joints, rarefaction of bone, a marked bleeding tendency, extravasation of blood into fascial layers, anemia, loosening or loss of the teeth, and poor wound healing.

B. Tests for Deficiency. Capillary resistance is reduced, and x-rays of the long bones may show typical changes. There is also a lowering of serum or white cell ascorbic acid levels.

C. Treatment. Give sodium ascorbate injection, 100-500 mg ( $1\frac{1}{2}$ -7 $\frac{1}{2}$  gr.) I.M., or ascorbic acid, 100-500 mg. orally daily as long as deficiency persists.

### OTHER VITAMINS

Many other vitamins have been described. Some are important in human nutrition and disease, most play an unknown role.

#### Pyridoxine Hydrochloride.

Pyridoxine may be important in transamination and decarboxylation of proteins. It may relieve nervous symptoms and weakness in pellagrins when niacin fails and may relieve glossitis and cheilosis when riboflavin fails. Its role (if any) in human atherosclerosis is uncertain. The dosage is 10-50 mg ( $\frac{1}{6}$ - $\frac{3}{4}$  gr.) I.V. or I.M. daily with other factors of the B complex.

#### Folic Acid (Pteroylglutamic Acid; L. casei Factor).

Folic acid seems to be essential for the metabolism of cell nuclear materials. It is effective in the treatment of certain macrocytic anemias.

#### Vitamin B<sub>12</sub> (L. lactis Dornier Factor).

Vitamin B<sub>12</sub> is a phosphorus- and cobalt-containing material isolated from purified liver extract. It is probably the effective principle (extrinsic factor) which is lacking in pernicious anemia.

## OBEISITY

Obesity may be defined as an increase in weight of over 10% above normal due to generalized deposition of fat in the body.

Normal weight is difficult to determine in clinical practice however the standard age height and weight tables may be used.

From a metabolic point of view all obesity has a common cause intake of more calories than are required for energy metabolism. The reasons for differences in the energy utilizations of various individuals which make it possible for one person to utilize his calories more efficiently than another are not known.

Although most cases of obesity are due to simple overeating a few endocrine disorders lead to specific types of obesity (e.g. Cushing's syndrome and hypothalamic lesions).

Hypothyroidism is rarely associated with obesity.

### Treatment

Specific weight reducing chemical agents and hormones singly or in combination are either ineffective or hazardous and have no place in the treatment of obesity.

**A Diet** Diet is the most important factor in the management of obesity. There are a number of points to consider.

**1 Calories** In order to lose weight it is necessary to decrease the intake to below the caloric requirements of the individual. One can determine a very approximate average daily weight loss with a given diet by the following formula:

$$\frac{\text{Approximate Daily Caloric Requirements} - \text{Number of Calories in Diet}}{4000}$$

$$= \text{Weight Loss in lb / Day}$$

The number of calories/day to prescribe for a patient varies with age, occupation, temperament, and the urgency of the need for weight reduction. A daily caloric intake of 800-1200 Calories is satisfactory for a reducing diet.

There is no evidence that supervised rapid weight loss is harmful. It has been shown that with adequate protein intake nitrogen balance can be maintained on 350-450 Calories/day. In these markedly restricted diets ketonuria may appear; it is usually very slight after the first few days, however, and acidosis has never been observed. In addition, since the patients realize they are on a diet, they of-

ten will adhere more willingly when they show rapid weight loss than when the results seem to be slow in appearing.

**2 Proteins** - A protein intake of at least 1 Gm / Kg should be maintained. If it is necessary to add protein to the low caloric diet, protein hydrolysate or casein (free of carbohydrate and fat) can be used.

**3 Carbohydrate and fat** - To keep the calories and ketosis down, fats are decreased. After the protein requirements have been met, most of the remaining diet is supplied from carbohydrates.

**4 Vitamins and minerals** Most reducing diets are likely to be deficient in vitamins but adequate in minerals. Therefore vitamins should be used to supply the average daily maintenance requirements during the time of weight reduction.

**5 Sodium restriction** - It has been shown that a normal person on a salt free diet will lose from 2-3 Kg (5-6 lb); this reduction is temporary and the weight will return when salt is added to the diet. The same is true of the obese patient and although an apparently dramatic effect can be obtained with salt free diets, it is of no permanent value.

### B Medication

**1 Appetite suppressants (anorexigenic drugs)** - Amphetamine sulfate (Benzedrine®) and dextro amphetamine sulfate (Dexedrine®) have proved of value in aiding patients on reducing regimens by decreasing the appetite and giving a sense of well-being. In proper doses these drugs are rarely contraindicated except in cardiovascular disease, especially hypertension, and in those patients in whom these drugs produce CNS stimulation. Because of their CNS-stimulating effects, it is wise to avoid causing insomnia by not giving these drugs in the evening.

These drugs are usually given twice a day, in the morning and early afternoon or one-half hour before breakfast and lunch. The dosages are as follows: Benzedrine® 5-10 mg b.i.d., Dexedrine® 2.5-5 mg b.i.d.

Other anorexia-producing drugs include phenmetrazine hydrochloride (Preludin®) 12.5-25 mg 2-3 times daily, phendimetrazine (Plegine®) 17.5-35 mg 2-3 times daily, and diethylpropion (Tenuate®) 25 mg 2-3 times daily.

**2 Drugs to speed up metabolism** - Note: There is no satisfactory drug to speed up metabolism. Thyroid has little or no place in the management of obesity. The low BMR associated with obesity is merely due to the fact that BMR is a measurement of oxygen consumption.

in terms of body surface area. The body surface area of obese patients is increased, but the increase is due to a relatively poor oxygen consumer (fatty tissue) rather than the other more active tissues, and so an apparently low BMR results. Actually, the basal caloric requirements of an obese person are greater than they would be if the same person were of normal weight, for fat tissues have a definite but slow metabolism. It has been shown that obese people with low BMR's can tolerate 0.2 Gm. (3 gr.) or more of thyroid/day without change in BMR. Prolonged administration of thyroid may suppress the patient's normal thyroid secretion.

**C. Exercise** Although exercise increases the energy output, extreme exercise is necessary to significantly alter weight. Playing 18 holes of golf, for instance, raises the total caloric requirements only by about 100-150 Calories. In addition, exercise tends to increase the appetite and may make it more difficult to control the diet properly.

**D. Psychologic Factors** Overeating is largely a matter of habit and may be associated with psychologic problems. Whatever the cause, the patient must be retrained in his eating habits and educated to understand that once his weight is normal he can easily become obese again by eating more than necessary.

## KWASHIORKOR

*Kwashiorkor is a nutritional deficiency syndrome which usually occurs in weaning infants (i.e., less than 2 years of age) but may occur in adolescents and adults as well. It is attributed to inadequate intake of proteins or perhaps of specific amino acids, but mineral (and probably vitamin) deficiencies also play a role. It is prevalent in Africa, Asia, southern Europe, and Central and South America, in areas where the protein content of the diet is deficient in amount or of poor quality (vegetable protein). Complicating tropical infections and infestations may aggravate the nutritional deficiency by curtailing the intake, decreasing the absorption, and increasing the demand. The liver shows the most marked pathologic changes: hepatic enlargement and fatty infiltration which may progress to a condition resembling portal cirrhosis. There is also atrophy of the pancreatic acini with loss of granules followed by fibrosis.*

*Kwashiorkor is characterized clinically by growth failure, irritability and apathy, rash, desquamation, skin hyperpigmentation or depigmentation, ulceration, cheilosis, stomatitis, conjunctivitis, sparse or depigmented hair, anorexia, vomiting, diarrhea, hepatomegaly, and edema. Blood changes include anemia, hypoalbuminemia, hyperglobulinemia, and low levels of alkaline phosphatase, urea, amylase, and lipase.*

*Prevention of the disease is a combined public health and socio-economic problem. Treatment consists of supplying an adequate intake of protein (8-10 Gm. protein/Kg.) of high biologic value (e.g., milk, eggs, meat) plus mineral and vitamin supplements. Concomitant infections require simultaneous treatment. It may be necessary to give transfusions of whole blood or plasma. If oral feeding is a problem, tube feeding may be necessary.*

*Without treatment, 50-75% of kwashiorkor victims die.*

*Moodie, A. Kwashiorkor: follow-up studies. J. Pediat 58:392-403, 1961.*

## HEREDITARY METABOLIC DISEASES

The concept of genetic control of metabolism has been recognized for more than 50 years, but the number of diseases which are now considered to be hereditary metabolic disorders has increased most rapidly during the past decade. Garrod's original description of 4 inborn errors of metabolism in 1908 was regarded with interest, but these disorders were largely considered to be rare medical curiosities of little clinical importance. The more than 300 hereditary metabolic disorders about which we now have at least some knowledge include common and uncommon, benign and serious diseases, metabolic disturbances involving almost every class of biochemical substance, and diseases of all organs and tissues of the body.

Information about metabolic abnormalities is not only of importance in furthering our understanding of disease processes, but is fundamental to a proper therapeutic approach to them. Old concepts of hereditary transmission of physical traits simply as dominant or recessive have had to be modified to explain the "asymptomatic carriers" of hereditary traits. Biochemical studies on relatives of patients with hereditary metabolic disorders

may reveal deficiencies not clinically manifest. Recognition of the heterozygote carrier may be of extreme value from a eugenic point of view (in preventing potentially incompatible matings) and from the standpoint of the health of the individual (by special dietary control, appropriate medication and avoidance of drug idiosyncrasies).

Determination of the genetic basis of metabolic disorders is made by a careful family history and appropriate biochemical studies on the patient and on available relatives. Biochemical studies may include the determination of essential blood constituents, abnormal protein molecules, specific enzymes, abnormal metabolites, electrolytes, renal transport mechanisms, and tolerance or restriction tests with food or chemicals.

Several of the hereditary metabolic disorders as they relate to specific organ systems are discussed in other sections of this book. Examples of other well known unusual, or recently described metabolic disorders are included in this chapter.

A glossary of genetic terms may be found in the Appendix (p. 808).

## DEFICIENCY OF PLASMA PROTEIN FRACTIONS

### Agammaglobulinemia & Hypoglobulinemia

Congenital agammaglobulinemia is a rare sex-linked recessive hereditary disorder due to deficiency or absence of gamma globulin. It occurs only in males and is manifest clinically by recurrent bacterial infections. The response to viral infections is usually normal. Immunologic responses (e.g., blood typing, immunization) fail to occur. The diagnosis is confirmed by demonstration of marked deficiency or absence of gamma globulin by electrophoretic or immunologic methods.

Treatment consists of monthly lifetime 1 M injections of 0.1 Gm./Kg. of human gamma globulin, early recognition of bacterial infections, and treatment at the time of infection with gamma globulin and appropriate anti-infective agents.

Secondary agammaglobulinemia (preferably referred to as hypoglobulinemia) occurs most commonly in older children or adults. It is usually secondary to one of the following diseases: (1) Diseases associated with hypoproteinemia (e.g., liver disease, nephrosis, malnutrition, congenital panhypoproteinemia, transient dysproteinemia) or (2) neoplastic diseases (e.g., multiple myeloma, lymphoma,

lymphatic leukemia). It usually manifests itself by recurrent infections, but immunologic response is usually present. Although the gamma globulins are decreased, they rarely fall to the very low or disappearance levels characteristic of primary agammaglobulinemia.

Treatment is directed at the primary disease, and gamma globulins are given as for primary agammaglobulinemia. Do not use antibiotics prophylactically, but treat infections with appropriate antibiotics as they occur.

Gitlin D., & others. The gamma globulins and their clinical significance. *New England J. Med.* 260:21-7, 1958.

### Analbuminemia

Congenital analbuminemia is a rare disorder caused by the failure to properly synthesize albumin. Serum albumin is low or absent and total serum proteins are low. Clinical findings consist of edema and hypotension.

Treatment consists of administering plasma or serum albumin.

Gordon R. S., Jr., & others. Idiopathic hypalbuminemia. *Ann. Int. Med.* 51:553-76, 1959.

## ABNORMALITY OF MOLECULAR STRUCTURE

### Methemoglobinemia

Congenital methemoglobinemia is caused either by a deficiency in the specific enzyme required in conversion of methemoglobin to hemoglobin or by the presence of an abnormal hemoglobin M. Clinically it is manifested by a persistent gray cyanosis not associated with cardiac or respiratory abnormality, and by easy fatigability, dyspnea, tachycardia, and dizziness with exertion. The venous blood is brown, the oxygen capacity of arterial blood is reduced, and excessive amounts of methemoglobin are present in the blood.

Continuous administration of methylene blue by mouth, 240 mg. daily, will relieve the symptoms and cyanosis in some cases. The prognosis for life is good.

Breakley V. K. St. G., Gibson Q. H., & D. C. Harrison. Familial idiopathic methemoglobinemia. *Lancet* 1:935-8, 1951.

## DISORDERS OF AMINO ACID METABOLISM

### Albinism

Albinism is a congenital disorder associated with the absence of tyrosinase in the melanocytes and manifest clinically by the absence of pigment in the skin, hair, and eyes. The skin and hair are white, the irides reddish and the pupils are red. Photophobia, nystagmus, and defective vision may occur.

There is no specific treatment.

Campbell, B., & L. Swift. Partial albinism.

J A M A 181:1103-7, 1962

Falls, H F. Albinism. Tr Am Acad Ophth 57:324-30, 1953

### Alkaptonuria

Alkaptonuria is a rare metabolic disorder inherited as a recessive trait. It is due to absence from the liver of an enzyme, homogentisic oxidase, which is necessary for the oxidation of homogentisic acid. Absence of the enzyme permits homogentisic acid to be excreted unmetabolized in the urine. Diapers or clothing may be stained with homogentisic acid in the urine. Staining of the cartilage of the nose and ears (ochronosis) may occur in older patients, sometimes causing cartilaginous degeneration of joints and severe arthritis. The urine test for homogentisic acid (with dilute ferric chloride solution) produces a transient deep blue color.

No specific treatment is available.

Galdston, M., Steele, J M., & K. Dobriner.

Alcaptonuria and ochronosis, with a report of three patients and metabolic studies in two. Am J Med 13:432-52, 1952

Martin, W J., & others. Alkaptonuria: report of 12 cases. Ann Int Med 42:1052-64, 1955

### Phenylketonuria (Phenylpyruvic Oligophrenia)

Phenylketonuria is a not uncommon metabolic disorder inherited as a recessive trait. It is due to absence of an enzyme, phenylalanine hydroxylase, which is capable of converting phenylalanine to tyrosine. Phenylalanine accumulates in the blood and the deamination product, phenylpyruvic acid, is excreted in the urine. If untreated, mental retardation and schizoid changes almost invariably occur, frequently to a marked degree. Patients are most often blue-eyed blonds and, because of pigmentary defects, are predisposed to photosensitivity and eczema. Physical development is usually normal. There may be signs of extrapyramidal involvement, with tremor,

ataxia, and hypertonicity in two-thirds of cases. Perspiration is usually excessive. Convulsions may occur. Encephalography may show frontal lobe atrophy. Phenylpyruvic acid may be demonstrated in the urine if a dark green color results when dilute ferric chloride is added to acidified urine. Serum phenylalanine levels are more definitive.

A diet low in phenylalanine, when started in the first few weeks of life, usually prevents mental retardation. In more established cases such a diet may occasionally arrest or improve the condition.

Horner, F.A., & others. Termination of dietary treatment of phenylketonuria. New England J Med 266:79-82, 1962

### Maple Sugar Urine Disease

Maple sugar urine disease is a rare familial disorder caused by the absence of amino acid decarboxylase, resulting in a disorder of metabolism of essential branched-chain amino acids. Symptoms appear in the first week of life and consist of spasticity, opisthotonos, irregular respirations, and feeding difficulties. The urine has a maple sugar odor.

No effective treatment is available. Death occurs within weeks to months.

Dancis, J., Levitz, M., & R G Westall. Maple syrup urine disease. Pediatrics 25:72-8, 1960

### Cystathioninuria

Cystathioninuria is a rare inborn disorder of amino acid metabolism probably related to a deficiency of cystathionine enzyme. It causes mental retardation. There is no known treatment.

### Glycinuria

Glycinuria is a genetic metabolic disorder due to a defective renal transport mechanism for glycine. It causes increased glycine excretion in the urine and a tendency toward nephrolithiasis. Otherwise health is unimpaired.

Treatment consists of adequate hydration. Low-protein diets are of questionable value.

### Cystinuria

Cystinuria is a hereditary metabolic disorder due to a defective renal transport mechanism for dibasic amino acids. Because of impaired renal tubular reabsorption of cystine, lysine, arginine, and ornithine, these dibasic amino acids are excreted in the urine. Since cystine is relatively insoluble in neutral or

acid solution, urinary calculi of almost pure cystine are common

Treatment is aimed at preventing stone formation by increasing the fluid intake and alkalinizing the urine. In severe cystinuria it may be necessary to control urinary excretion of cystine by administration of a low-methionine (and low cystine) diet

Smith, D R , Koib, F O , & H A Harper  
The management of cystinuria and cystine-stone disease J Urol 81 61-71, 1959

#### Fanconi's Syndrome

Fanconi's syndrome is a hereditary metabolic disorder, presumably of multiple causes and associated with multiple defects of the renal transport mechanisms. It is manifested clinically by emaciation, dwarfism, renal rickets or osteomalacia (resistant to vitamin D in the usual doses), dehydration, hypophosphatemia, spontaneous fractures, polyuria, aminoaciduria, proteinuria, and glycosuria. The disorder may not become evident until adult life and should be suspected in any case of spontaneous fracture, glycosuria, and aminoaciduria.

Treatment, which is usually ineffective, consists of giving large doses of vitamin D, alkalinization of the urine with sodium or potassium bicarbonate, and adequate hydration. Patients usually die of renal failure.

Chiselm, J J , Jr The clinical significance of aminoaciduria J Pediat 55 303-14, 1959

Harper, H A , & others Renal aminoaciduria. Report of two cases, with studies of amino acid excretion patterns Am J Dis Child 84 327-39, 1952

#### Hartnup's Disease (H Disease)

Hartnup's disease is a rare genetic defect in the renal transport mechanism for tryptophan. Clinical findings consist of dermatitis, cerebellar ataxia, mental retardation, aminoaciduria, and increased excretion of indole and indican compounds.

Treatment consists of hydration to prevent the formation of renal calculi. Dietary protein restriction and treatment with niacinamide are of questionable value.

#### Leucine Sensitivity Disease

Leucine sensitivity disease is a genetic metabolic disorder characterized by abnormal hypoglycemia and is due to leucine sensitivity. Clinically it is manifest as hypoglycemia, flushing, sweating, and convulsions.

No specific treatment is available.

Cochrane, W A , & others Familial hypoglycemia precipitated by amino acids J Clin Invest 35 411-22, 1956

### DISORDERS OF CARBOHYDRATE METABOLISM

#### Fructosuria.

Fructosuria is an inborn error of metabolism which is probably due to a deficiency of the enzyme fructokinase, resulting in elevated blood levels of fructose and excretion of fructose in the urine. There are no clinical manifestations, and no treatment is necessary. However, if the diet contains large quantities of foods rich in fructose and sucrose, a considerable proportion of dietary carbohydrate may be lost.

Lenzner, A R Fructosuria: report of a case Ann Int Med 45 702-8, 1956

#### Galactosemia

Galactosemia is an inborn error of metabolism which is due to a deficiency of the enzyme galactose-1-phosphate uridyl transferase. This enzyme is necessary for the conversion of galactose to glucose. Clinically the disorder becomes manifest soon after birth by feeding problems, vomiting, diarrhea, abdominal distention, hepatomegaly, jaundice, cataracts, mental retardation, and elevated blood and urine galactose levels.

Exclusion from the diet of milk and all foods containing galactose and lactose for the first three years of life will prevent the above manifestations if instituted before the fourth month, and will bring about improvement in those patients in whom symptoms and signs have already appeared.

Donnell, G N , Bergren, W R , & R S  
Cleland Galactosemia P Clin North America 7 315-32, 1960

#### Von Gierke's Disease

Von Gierke's disease is a rare inborn error of metabolism characterized by the excessive deposition of glycogen in the liver and kidney, secondary to a deficiency of the enzyme glucose-6-phosphatase, which is required for the degradation of glycogen to glucose. The disorder becomes manifest in infancy or early childhood by easy fatigability, hepatomegaly (glycogen deposition) and hypoglycemia and ketosis (unavailability of glucose) with resulting shock and convulsions. The serum glucose does not respond to the epinephrine test.



Treatment is directed toward improvement of nutrition and correction of the hypoglycemia by frequent feedings. Corticotropin or the corticosteroids may be of some value. Death usually occurs in infancy or childhood, but if the patient survives this period the symptoms usually improve as the child grows older.

Leading article. Diseases of glycogen storage. *Lancet* 1:206-7, 1961

#### McArdle's Syndrome.

McArdle's syndrome is a hereditary absence of muscle phosphorylase, resulting in an inability to convert glycogen to glucose in muscle. Clinically there are no symptoms other than a myopathy characterized by weakness, stiffness, pain, and prolonged contraction of the skeletal muscles with moderate exercise. A transient myoglobinuria is noted. This myopathy is not evident in resting muscle.

Treatment consists of limitation of physical exercise and adequate diet. Glucagon 1 M 3 times a day has been reported to be of value.

Schmid, R., & L. Hammaker. Hereditary absence of muscle phosphorylase. *New England J Med* 264:223-6, 1961

#### Pentosuria

Pentosuria is a rare inborn error of metabolism due to the absence of xylulose reductase, resulting in the excretion of pentoses in the urine and a positive reduction test. It is benign and asymptomatic and requires no treatment.

Bozian, R. C., & P. Touster. Essential pentosuria: renal or enzymic disorder. *Nature* 184:463-4, 1959

### DISTURBANCES OF LIPID METABOLISM

#### Gaucher's Disease.

Gaucher's disease is a familial disorder of excess ceramide storage in the reticuloendothelial cells. Proliferation of these abnormal cells causes progressive hepatomegaly, splenomegaly, and skeletal lesions, with bone fracture at the site of the lesions. The disease may have its onset at any age, although onset is usually in childhood. Anemia, jaundice, thrombocytopenia, and at times neurologic lesions may also be present. The course of the disease is variable. In children it usually progresses rapidly, resulting in death in

a few months, in older adults, it progresses so slowly that the patient often dies of intercurrent disease.

Treatment is supportive. Splenectomy is indicated only when hypersplenism develops.

Asia, D. Y.-Y., Naylor, J., & J. A. Bigler. Gaucher's disease: report of two cases in father and son and review of the literature. *New England J Med* 261:164-9, 1959.  
Levin, B. Gaucher's disease, clinical and roentgenologic manifestations. *Am J. Roentgenol* 85:685-96, 1961

#### Lipogranulomatosis.

Lipogranulomatosis is a congenital disorder of lipid metabolism due to excessive storage of lipoglycoprotein in the subcutaneous and periarthritic tissues. It becomes manifest shortly after birth by sensitivity and swelling of the extremities and a hoarse, weak cry. There is a progressively severe generalized involvement of the joints associated with subcutaneous and periarthritic nodules. Fixation of the laryngeal cartilage results in dysphonia, and pulmonary infiltration produces dyspnea. Fever is variable.

There is no known effective treatment.

Farber, S., Cohen, J., & L. L. Uzman. Lipogranulomatosis. *J Mt Sinai Hosp* 24:818-37, 1957

#### Neimann-Pick Disease (Sphingomyelin Lipidosis).

Neimann-Pick disease is a rare, genetically determined, recessive disorder characterized by the excessive storage of phospholipids, especially sphingomyelin, in the reticuloendothelial system. Manifestations occur early in infancy and consist primarily of hepatosplenomegaly and CNS involvement, with mental retardation and convulsions. Other symptoms and signs include diffuse pulmonary infiltrations, cutaneous lesions, a cherry-red macular spot, gastrointestinal bleeding, lymph node enlargement, thrombocytopenia, anemia, and foam cells in hepatic or marrow biopsies.

Treatment is supportive. Death usually occurs during childhood.

Crocker, A. C., & S. Farber. Neimann-Pick disease. A review of eighteen patients. *Medicine* 37:1-95, 1958

#### Plasma Lipid Disturbance (Bigler).

Plasma lipid disturbance is a hereditary lipid disorder manifested by an increase of phospholipids and triglycerides in the plasma, resulting in physical and mental retardation and hepatomegaly.

Treatment is symptomatic.

Bigler, J. A., & others: An inborn error of lipid metabolism. *Pediatrics* 23 644-61, 1959

### Familial Essential Xanthomatosis.

Familial essential xanthomatosis is a genetically determined dominant disorder characterized by the excessive storage of cholesterol and its esters in the reticuloendothelial system. Cholesterol is deposited in the skin (xanthoma tuberosum et planum) blood vessels, eyelids (xanthelasma) endocardium and tendons. Premature arteriosclerosis and myocardial infarctions are common. The total and esterified serum cholesterol is elevated.

Treatment consists of the use of polyunsaturated fats in the diet and possibly the use of the various commercially available oral cholesterol-lowering agents. Surgical removal of deposits may be required when they interfere with function or for cosmetic reasons (xanthelasma).

Guravich, J. L. Familial hypercholesterolemia xanthomatosis. *Am J Med* 26 8 29 1959

## DISORDERS OF PORPHYRIN METABOLISM

The porphyrins are cyclic compounds containing 4 pyrrole rings which are the precursors of hemoglobin and of other important enzymes and pigments. Heme is the complex of iron and porphyrin which unites with the protein globin to form hemoglobin. Disorders of porphyrin metabolism, which may be hereditary or acquired, are due to disturbances in the anabolic sequence of porphyrin metabolism. Several porphyric syndromes are recognized: (1) hereditary porphyrias, either hepatic (hepatogenic) or erythropoietic (congenital), and (2) acquired porphyria.

### Hepatic Porphyrias

The hepatic porphyrias are mendelian-dominant hereditary disorders characterized by excessive production of porphyrins and related compounds by the liver. They become clinically and biochemically manifest only after puberty. Mixed or combined hepatic porphyrias may occur. The porphyric trait, as manifested biochemically, may exist in completely asymptomatic individuals.

A Acute, Intermittent Porphyria. This is the most common type of porphyria. It is

characterized by attacks of gastrointestinal symptoms (abdominal colic, vomiting, and constipation), CNS symptoms (flaccid paralysis, peripheral neuritis, psychic disturbances and convulsions), and sinus tachycardia. Photosensitivity does not occur. The urine, which contains porphobilinogen, is often colorless when freshly voided, but may darken on standing or when exposed to ultraviolet light. The modified Ehrlich test of the urine (Watson-Schwarz test) is positive. Type III coproporphyrin and uroporphyrin may be excreted in the urine in large quantities. Acute attacks may be precipitated by barbiturates, alcohol and many other chemicals, as well as by menses, pregnancy (postpartum) infections and psychic trauma.

Treatment is nonspecific. Phenothiazine drugs given early in the attack may lessen the severity of symptoms. All other drugs or toxins (especially barbiturates and alcohol) must be avoided.

The over-all mortality rate is 15-20%. Death usually occurs as a result of motor paralysis during an acute attack. Most patients, however, survive acute attacks, and the prognosis for life is much better than was formerly believed.

B Porphyria Cutanea Tarda. This type occurs most commonly in middle-aged persons. Although it is usually hereditary, it may occur secondary to other liver disorders. There is varying photosensitivity of the skin, resulting in eczema, vesicles, and bullae. The hepatic content of porphyrin is greatly increased and liver function is impaired. Mild jaundice may be present. There is no porphobilinogen in the urine, but there is an abnormally high excretion of uroporphyrin and coproporphyrin.

Treatment consists of protection of skin from strong light and complete abstinence from alcohol.

### Erythropoietic Porphyria.

This is a rare inherited disorder transmitted as a mendelian-recessive trait. It is usually evident from birth and is due to an abnormality of developing normoblasts in the bone marrow which causes increased production of porphyrin. It is characterized by red urine, pink teeth which fluoresce with ultraviolet light, cutaneous photosensitivity with resultant vesicles, bullae, and scarring and pigmentation of the skin, hepatosplenomegaly, and anemia. Porphobilinogen is absent from the urine but there are large amounts of type I coproporphyrin and uroporphyrin in the feces and urine.

Treatment consists of protection against sunlight and ultraviolet light, splenectomy may sometimes be of value when hemolysis is present

#### Acquired (Secondary) Porphyrinurias

Secondary or "symptomatic" porphyrias (coproporphyrinurias) may follow poisoning with lead or other heavy metals and many other organic and inorganic poisons. They may also occur in the hemolytic and pernicious anemias, parenchymal liver disease, obstructive jaundice, the collagen diseases, and CNS disorders

Kark, R M Clinical aspects of the major porphyrinopathies M Clin North America 39 11-30, 1955

Martin W J, & F J Heck The porphyrias and porphyria A review of 81 cases Am J Med 20 239-50, 1956

Watson C J Porphyria Advances Int Med 6 235 99, 1954

Watson C J The problem of porphyria New England J Med 263 1205 15, 1960

### MISCELLANEOUS OTHER METABOLIC DISORDERS

#### Cystic Fibrosis

Pancreatic cystic fibrosis is a recessive inherited disease causing dysfunction of the exocrine glands of the pancreas, respiratory system, and sweat glands. It usually begins in infancy and is manifested by steatorrhea, malnutrition, repeated pulmonary infections, bronchitis, viscid sputum, and excessive sodium and chloride loss in the sweat (leading often to heat exhaustion in hot weather or during febrile episodes). Pancreatic enzymes are present in decreased amounts in the stools.

Treatment consists of a high-protein diet, moderate fat restriction, high doses of vitamin A, and pancreatin to aid digestion. Infections (especially respiratory infections) should be guarded against and treated promptly with antibiotics when they occur.

The disease is not curable, but since its recognition as a disease is only recent, long-term survival figures are not available.

Schwachman, H, & L L Kulczycki Long term study of 105 patients with cystic fibrosis Am J Dis Child 96 6-15, 1958

#### Gargoylism (Hurler's Syndrome)

Gargoylism is a rare hereditary metabolic disorder associated with the accumulation of

mucopolysaccharide in the tissue. It results in grotesque facies, mental deficiency, changes in bone shape, widening of sutures, corneal opacities, and finally heart failure. Dwarfism is usually present. The clinical features occur early, remain unchanged for years, and are most frequently found in incomplete clinical forms.

Treatment is symptomatic.

Dorfman, A, & A E Lorincz Occurrence of urinary acid mucopolysaccharides in the Hurler syndrome Proc Nat Acad Sci (U S ) 43 443-6, 1957

#### Primary (Idiopathic) Hemochromatosis

Primary hemochromatosis is a rare hereditary metabolic disorder characterized by the generalized deposition of hemosiderin in the tissues, especially the liver and pancreas. The disorder is presumably due to a metabolic fault which permits the accumulation of iron in the body following excessive absorption of iron from the intestine. It occurs almost exclusively in males between the ages of 50 and 60. Clinically there is bronzing of the skin, a nodular firm enlarged liver, and manifestations of cirrhosis and severe diabetes. Myocardial fibrosis leading to heart failure is not uncommon.

Treatment consists of removal of the excess iron by repeated phlebotomies or chelating agents and treatment of diabetes mellitus.

Rather, L J Hemochromatosis and hemosiderosis Am J Med 21 857-66, 1956

#### Primary Hyperoxaluria (Oxalosis)

Primary hyperoxaluria is a rare hereditary metabolic disease characterized by a continuously high urinary excretion of oxalate (unrelated to dietary intake of oxalate). It is probably related to a defect in glycine metabolism. Clinically it is manifested by progressive bilateral calcium oxalate urolithiasis, nephrocalcinosis, and recurrent urinary tract infections. Death usually occurs early as a result of renal failure or hypertension.

There is no specific treatment, although hydration to increase solubility may be of some help.

Daniels, H A, & others Familial hyperoxaluria Report of a family, review of the literature Am J Med 29 820-31, 1960

Stauffer, M Oxalosis report of a case, with a review of the literature and discussion of the pathogenesis New England J Med 263 386-90, 1960

### Marfan's Syndrome

Marfan's syndrome is a mendelian-dominant hereditary disorder of connective tissue, the basic metabolic defect of which remains unknown. The disease involves primarily the skeletal system, the cardiovascular system, and the eyes, but there are many other clinical manifestations. These patients are tall and thin. The extremities are long in relation to the trunk, the hands are spider-like (arachnodactyly) with thin tapered webbed fingers. Pes planus, pes cavus, and hammer toes may be present. Tower skull (long narrow and pointed head) and a high palatal arch are common findings. Winging of the scapulas and pigeon or funnel chests may occur. Dislocation of the lens (ectopia lentis), myopia, detached retinas, and other ocular abnormalities may be present. Cardiovascular deformities may include dilatation of the aorta and pulmonary arteries with resultant valvular insufficiency, dissecting aneurysm, and occasionally atrial septal defect. Serum mucoproteins are low and urinary excretion of hydroxyproline is increased. Mild incomplete (atypical) forms of the disease may exist.

Treatment is directed toward cardiovascular complications and is otherwise merely symptomatic and supportive.

Mortality during infancy is high. Death is usually due to cardiac complications.

Rosark, J. W. The Marfan syndrome: report of one case with autopsy, special histological study, and review of the literature. *Arch. Int. Med.* 103:123-32, 1959.

### AMYLOIDOSIS

Amyloidosis is a poorly understood disorder of protein metabolism which usually occurs secondary to chronic suppurative disease but which may also occur as the so-called 'primary' type in patients without apparent preexisting disease. The onset is insidious, and the clinical manifestations may vary widely depending upon the organs or tissues in which the peculiar homogeneous amorphous, proteinaceous amyloid substance is deposited. There appears to be some relationship between amyloidosis and the various other diseases associated with abnormalities of the serum globulin (e.g., multiple myeloma).

Four clinical types of amyloidosis have been described:

(1) Primary systemic amyloidosis, a rare disorder, occurs in patients without known preexisting disease. Amyloid is deposited chiefly in mesenchymal tissues with resultant involvement of many organs. It is characterized by weakness, weight loss, purpura, macroglossia, lymphadenopathy, hepatosplenomegaly, congestive heart failure, nephrotic syndrome, and abnormality of serum proteins.

(2) Amyloidosis associated with multiple myeloma may be a variation of the primary systemic type, but the relationship is uncertain.

(3) Primary localized (tumor-forming) amyloidosis is a rare disorder involving the upper respiratory tract (e.g., the larynx) again in the absence of preexisting disease and without evidence of amyloidosis in other tissues.

(4) Secondary amyloidosis, the most common type, is associated with chronic suppurative disorders. Amyloid is deposited widely in parenchymatous organs. (The liver, spleen, kidneys, and adrenal glands are most frequently involved.) Tuberculosis is the most common predisposing cause, but the condition may also follow chronic osteomyelitis and other chronic wasting and suppurative disorders.

The diagnosis of amyloidosis is based first on a suspicion that it may be present, since clinical manifestations may be varied and atypical. Preexisting long-standing infection or debilitating illness should suggest the possibility of its existence. Microscopic examination of biopsy or surgical specimens after suitable staining procedures is diagnostic. I.V. injection of Congo red in patients with systemic amyloidosis results in a 80-100% disappearance of the dye within one hour (normally less than 40% is removed).

Treatment of localized amyloid "tumors" is by surgical excision. There is no effective treatment of systemic amyloidosis and death usually occurs within 1-3 years. Early and adequate treatment of pyogenic infections will probably prevent much secondary amyloidosis. Since the advent of antibiotic and other anti-infective drugs for the treatment of infection, the incidence of amyloidosis is expected to decline.

Briggs, G. W. Amyloidosis. *Ann. Int. Med.* 55:943-57, 1961.

Rukavina, J. G., & others. Primary systemic amyloidosis: a review and an experimental, genetic, and clinical study of 29 cases. *Medicine* 35:239-34, 1956.

Wald, M H Clinical studies of secondary amyloidosis in tuberculosis Ann Int Med 43 383-95, 1955

## RETICULOENDOTHELIOSIS

The reticuloendothelioses include several so called distinct clinical diseases eosinophilic granuloma, Hand-Schüller Christian disease, and Letterer-Siwe disease There is some feeling, however, that because the pathologic findings are similar and because some transitional cases have been reported, these clinical syndromes may actually represent different phases or stages of the same disease

The reticuloendothelioses are not familial, and their etiology has not been determined

### Eosinophilic Granuloma.

Eosinophilic granuloma is a relatively benign disorder of the reticuloendothelial system which usually occurs in children but may occur at any age The characteristic skeletal lesions, which begin in the marrow, show proliferation of eosinophils and histiocytes Eventually the lesion erodes the body cortex, causing an enlargement in the area of involvement The lesions may be solitary or multiple, and usually occur in the skull and in the bones of the trunk and proximal portions of the extremities The granulomas may be quite painful, and pathologic fracture may occur Fever, leukocytosis, eosinophilia skin lesions, lymphadenopathy, and pleurisy or interstitial pulmonary infiltrations occasionally occur X-rays show rounded areas of bony rarefaction, often punched-out The diagnosis is established by biopsy

Treatment, consisting of curettage, excision, or x-ray therapy, is quite successful

### Letterer-Siwe Disease

Letterer-Siwe disease is a usually rapidly progressive and fatal disorder of the reticuloendothelial system which occurs most frequently in infancy or early childhood and, rarely, in young adults The pathologic lesions consist of widespread proliferation of histiocytes which may involve bone, but to a much greater extent than eosinophilic granuloma involves the skin lymph nodes and viscera as well Clinical manifestations include fever, anemia, hemorrhagic tendency, lymphadenopathy, hepatosplenomegaly, and skeletal and variable cutaneous lesions The diagnosis is made by biopsy of bone marrow or lymph nodes which

show characteristic nonlipid-containing histiocytes

Treatment is symptomatic and supportive Antibiotics may be required for the treatment of secondary infection Corticosteroids have not been of value X-rays may halt the progress of bone lesions

### Hand-Schüller-Christian Disease (Cranial Xanthomatosis).

Hand-Schüller Christian disease is a chronic disorder of the reticuloendothelial system characterized by lipid cell hyperplasia and proliferation of histiocytes The onset is in early childhood Classical clinical features include unilateral or bilateral exophthalmos, softened areas of the skull and other membranous bones, and diabetes insipidus Otitis media is a common presenting complaint Multiple small cutaneous plaques may appear on the skin, often resembling seborrheic dermatitis Lymphadenopathy, hepatosplenomegaly, and anemia often occur Blood cholesterol levels are often normal Bony defects in the skull and flat bones are readily seen on x-ray

No specific treatment is available although low fat diets have been recommended The course is chronic and relatively benign unless there is extensive involvement of vital organs X-ray therapy may be of value in the treatment of specific local lesions

Avery, M E , McAfee, J G , & H Q Guild  
The course and prognosis of reticuloendotheliosis Am J Med 22 636-52, 1957

## CRYOGLOBULINEMIA

Cold precipitable serum globulins have been demonstrated to a greater or lesser degree in a wide variety of disease states (e g , collagen diseases, chronic bacterial or protozoal infections, leukemias, lymphomas, and multiple myeloma), and in a few cases no primary cause can be determined The cryoglobulins resemble normal gamma globulin except for their propensity to precipitate when exposed to lowered temperatures The finding of cryoglobulinemia is often without any apparent significance It is assumed that when symptoms do occur as a result of cryoglobulinemia, the abnormal protein, on cooling precipitates in smaller vessels and causes increased viscosity, stasis thrombosis or hemorrhage

Clinical manifestations may include a Raynaud-like phenomenon on exposure to cold, oronasal bleeding, purpura, petechiae, retinal vascular constriction and hemorrhage, urticaria, and mottling, ulcerations, necrosis, and gangrene, especially in dependent areas. Cryoglobulins in significant concentrations (30 mg /100 ml ) may be demonstrated in the blood.

Treatment consists of preventing exposure to cold and, when possible, treatment of the underlying disease. In general, treatment is unsatisfactory.

Farmer, R G , Cooper, T P , & C A  
Pascuzzi Arch Int Med 106 483-59, 1980

### MACROGLOBULINEMIA

Macroglobulinemia is a rare chronic disorder of unknown cause characterized by the

formation of abnormal serum proteins of large molecular weight, weakness, weight loss, frequent infections, pallor, lymphadenopathy, hepatosplenomegaly, osteoporosis, edema, Raynaud's phenomenon, bleeding tendency, and usually a markedly increased erythrocyte sedimentation rate. It may occur in a so-called primary form or may be secondary to (or associated with) leukemia, multiple myeloma, lymphoma, sarcoma, carcinoma, chronic granulomatous infections, chronic liver or kidney disease, collagen disease, amyloidosis and cryoglobulinemia. Serum macroglobulins may be demonstrated by characteristic physicochemical electrophoretic and ultracentrifugal patterns.

Treatment, which is symptomatic and supportive, is usually ineffective. The course and prognosis of secondary macroglobulinemias are those of the underlying disease.

Ritzman, S E , & others. The syndrome of macroglobulinemia Arch Int Med 105 939-65 1960

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Hala, D Y-Y. Medical genetics. New England J Med 262 1172-8 1222 7, 1273 8, and 1313-23 1960

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Osborne, R H (editor). Genetic Perspectives in Disease Resistance and Susceptibility. Conference Bulletin, Annals of New York Academy of Science, Vol 91, Art 3, 1961

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# Infectious Diseases: Viral & Rickettsial

Henry Brainerd, J. Ralph Audy, & Leon Lewis

## VIRAL DISEASES

### RUBEOLA (Measles)

#### Essentials of Diagnosis

- Prodrome of fever, coryza, cough, conjunctivitis, photophobia, Koplik's spots.
- Rash brick-red, irregular, maculopapular, onset 4 days after onset of prodrome, face to trunk to extremities
- Leukopenia
- Exposure 14 days before rash

There is usually little difficulty in diagnosis when the complete clinical course is viewed. During the prodromal stage measles may be mistaken for an acute respiratory infection, the rash may be confused with drug rash, infectious mononucleosis, or the other exanthematous diseases.

#### General Considerations.

Measles is a systemic viral infection transmitted by inhalation of infective droplets. Its highest age incidence is in young children. One attack confers permanent immunity. Communicability is greatest during the pre-eruptive stage, but continues as long as the rash remains.

#### Clinical Findings.

A Symptoms and Signs. Fever is often as high as 40-40.5°C. (104-105°F). It persists through the prodrome and rash (about 7 days), but may remit briefly at the onset of rash. Malaise may be marked. Coryza resembles that seen with upper respiratory infections (nasal obstruction, sneezing, and sore throat). Cough is usually persistent and non-

productive, and arouses the suspicion of pneumonia. Conjunctivitis, with redness, swelling, photophobia, and discharge, aids in distinguishing measles from respiratory infections.

Koplik's spots usually appear about 2 days before the rash and last about 4 days. They appear as tiny "table salt crystals" on the dull red mucous membranes of the inner aspect of the cheeks and often on the inner conjunctival folds and vaginal mucous membranes. They are pathognomonic of measles. The mucous membranes are erythematous. A yellowish exudate may appear on the tonsils. The tongue is coated in the center, the tip and margins are red. Moderate generalized lymphadenopathy is common. Splenomegaly occurs occasionally.

The rash usually appears first on the face and behind the ears 4 days after the onset of symptoms. The initial lesions are pinhead-sized papules which coalesce to form the brick-red, irregular, blotchy maculopapular rash which may further coalesce in severe cases to form an almost uniform erythema on some areas of the body. By the second day the rash begins to coalesce on the face as it appears on the trunk. On the third day the rash is confluent on the trunk and begins to appear on the extremities. The rash begins to fade on the face on the third day and thereafter fades in the order of its appearance. Hyperpigmentation remains in fair-skinned individuals and severe cases. Slight desquamation may follow.

B Laboratory Findings. Leukopenia is usually present unless secondary bacterial complications exist. Febrile proteinuria is present.

#### Complications.

Secondary bacterial infections are common. Streptococcal, staphylococcal, pneumococcal, and other infections should be suspected if fever persists after the rash has

munity The incubation period is 14-21 days (average 16) The period of communicability is not known but the disease is probably transmissible before the rash appears

### Clinical Findings

**A Symptoms and Signs** Fever and malaise usually mild may precede the eruption by one day Mild coryza may be present Pain and tenderness in the posterior cervical lymph nodes may precede the rash Joint pain is occasionally prominent in adults

Posterior cervical and postauricular lymphadenopathy is very common Erythema of the palate and throat sometimes blotchy may be noted A fine pink maculopapular rash appears on the face trunk and extremities in rapid progression (2-3 days) and fades quickly usually lasting one day in each area

**B Laboratory Findings** Leukopenia may be present early and may be followed by an increase in plasma cells

### Complications

Fetal abnormalities constitute a serious threat in rubella occurring during the first trimester of pregnancy Encephalitis thrombocytopenic purpura and streptococcal pharyngitis and adenitis occur rarely

### Prevention

Pregnant women who have been exposed to rubella should be given 5-20 ml of immune serum globulin (gamma globulin) 1 M in an effort to prevent or modify the disease

### Treatment

**A General Measures** Aspirin as required for symptomatic relief

**B Treatment of Complications** Encephalitis and thrombocytopenic purpura can only be treated symptomatically Secondary streptococcal pharyngitis should be treated with penicillin

### Prognosis

The illness rarely lasts longer than 3-4 days Fatality is extremely rare

Inglis T H & others Preventive medicine and epidemiology rubella its epidemiology and teratology Am J M Sc 239 363 83 1960

## CYTOMEGALIC INCLUSION DISEASE

Cytomegalic inclusion disease is a viral infection usually latent in infants and children Clinically apparent infections occur in newborn infants following transplacental transmission and are manifested by jaundice hemolytic erythroblastic anemia thrombocytopenia with a hemorrhagic tendency hepatosplenomegaly chorioretinitis encephalitis and microcephaly The disease may occur also in older children debilitated by other illnesses Typical cytomegalic cells may be isolated from the urine or adenoids in both clinical and latent cases

No treatment is available Clinically apparent cytomegalic inclusion disease is usually fatal

## VARICELLA (Chickenpox)

### Essentials of Diagnosis

- Mild symptoms (fever malaise) just preceding or simultaneous with eruption
- Rash pruritic centripetal papular changing to vesicular pustular and finally crusting
- Leukopenia
- Exposure 14-20 days previously

Occurrence mainly in children with a history of exposure about 2 weeks previously aids in differentiating varicella from pemphigus dermatitis herpetiformis and pustular syphilis distribution distinguishes it from herpes zoster and smallpox

### General Considerations

Varicella is a viral disease spread by inhalations of infective droplets or crusts Most cases occur in children One attack confers permanent immunity The virus is related to that of herpes zoster The incubation period is 10-20 days (average 14 days)

### Clinical Findings

**A Symptoms and Signs** Fever and malaise are usually mild in children more severe in adults Itching is characteristic of the eruption Vesicular lesions quickly rupturing to form small ulcers may appear first in the oropharynx The rash is most prominent on the face scalp and trunk but to s



lesser extent commonly involves the extremities (centripetal). Maculopapules are succeeded in a few hours by vesicles which quickly become pustular and eventually form crusts. New lesions may erupt for 1-5 days (usually 3 days), so that all stages of the eruption are generally present simultaneously. The crusts usually slough in 7-14 days. The vesicles and pustules are superficial, elliptical, and have slightly serrated borders.

**B Laboratory Findings** Leukopenia is commonly present. Multinucleated giant cells may be found in scrapings of the base of the vesicles.

#### Complications.

Secondary bacterial infection of the lesions is common and may produce a pitted scar. Cellulitis, erysipelas, or surgical scarlet fever may occur.

Pneumonia may be due to varicella virus or secondary bacterial infection.

Encephalitis may follow the eruption.

Death may occur in patients receiving corticosteroid therapy.

#### Prevention.

Temporary passive protection irregularly follows I M. administration of 20 ml of convalescent serum, but this is rarely warranted.

#### Treatment.

**A General Measures** Isolate the patient until primary crusts have disappeared and keep at bed rest until afebrile. Keep the skin clean by means of frequent tub baths or showers when afebrile. Calamine lotion locally and antihistamines orally may relieve the pruritus.

**B. Treatment of Complications** Secondary bacterial infection of the lesions may be treated with bacitracin or tyrothricin ointment locally, if extensive, penicillin I. M. may be given. Postvaricella encephalitis and varicella pneumonia may be treated only symptomatically. Bacterial pneumonia is treated with appropriate antibiotics.

#### Prognosis.

The total duration from onset of symptoms to the disappearance of crusts rarely exceeds 2 weeks. Fatalities are rare.

Weinstein, L., & R.H. Meade; Respiratory manifestation of chickenpox: special consideration of the features of primary varicella pneumonia Arch. Int. Med 98:91-9, 1956.

## VARIOLA (Smallpox)

#### Essentials of Diagnosis

- \* Severe symptoms (headache, nausea, fever, prostration) precede eruption by 2-4 days.
- \* Centrifugal macular rash, changing to papular, vesicular, and pustular, and finally crusting and occasionally hemorrhagic eruptions of similar stage in any given area.
- \* Leukopenia early, leukocytosis late.
- \* Exposure 7-21 days previously (usually 10-14 days)

The pre-eruptive stage may be mistaken for an acute respiratory infection the eruptive stage may be mistaken for chickenpox. The rash must be distinguished from that of rickettsialpox, syphilis, measles, Kaposi's varicelliform eruption, and drug sensitivity.

#### General Considerations.

Smallpox is a highly contagious viral disease transmitted by droplets or by contact with infected crusts. All ages are susceptible depending upon the interval since vaccination. Previous effective vaccination prevents or modifies the disease (varioloïd). Variola major is more virulent than variola minor (alastrim). The incubation period is 7-21 days (average 12 days)

#### Clinical Findings.

**A Symptoms and Signs** Fever, usually 38.0-40.6°C. (102-105°F) appears 2-4 days before the eruption and may abate temporarily at the beginning of eruption to increase again during the stage of pustule formation. Malaise and prostration are usually marked. Headache and low backache are characteristically severe. Nausea and vomiting, dizziness, and constipation may occur.

Erythematous, hemorrhagic, or morbilliform rashes occasionally occur during the prodromal illness. The rash appears first on the face and scalp, then on the wrists, hands, neck, back, chest, arms, legs, and feet. New lesions appear for 2-3 days. Pink macules rapidly become papules, which become vesicles in about 3 days. On about the sixth day of eruption, the vesicles become pustules, these in turn become crusts on the eleventh or twelfth day. Marked edema and oozing may occur during the stage of pustule

**formation** The crusts may persist for a week or longer, especially on the palms and soles. The individual lesions are round and deeply set in the skin, giving a shotty sensation upon palpation. The distribution of the lesions, even in mild cases is centrifugal, with lesions densest on the face and distal portions of the extremities. In milder cases the lesions are discrete, in severe cases they may be confluent. The lesions in any given area tend to be of a similar stage of evolution.

Lesions on the mucous membranes may precede the exanthem by a short interval.

The initial eruption may be hemorrhagic and accompanied by hemorrhage from mucous membranes. This type is invariably fatal. Delayed hemorrhage (less often fatal) may occur into the vesicles or pustules.

**B. Laboratory Findings** Leukopenia may occur during the early stages, succeeded by leukocytosis during the stage of pustule formation. Proteinuria is common. The film test of Van Rooyen and Dlingworth is positive if elementary bodies can be demonstrated on a smear of scraping of early lesions stained by the Paachen method. The rabbit eye test of Paul is positive if vesicular and necrotizing lesions appear on a rabbit cornea 36-48 hours after scarification with a needle dipped in vesicular or pustular fluid.

Chick embryo inoculation is positive if a pock appears on chick chorio-allantois inoculated with blood or fluid from lesion.

Complement fixation and flocculation tests with pock material and specific immune sera are available.

Complement-fixing and chicken erythrocyte agglutinating inhibiting antibodies appear during or after the second week of the disease.

### Complications

Secondary infection of the lesions is the rule. Residual pitting is common. Erysipelas, surgical scarlet fever, or gangrene may occur. Septicemia, often streptococcal, may occur. Respiratory obstruction may occur due to laryngeal lesions.

### Prevention.

Vaccination. (See Vaccinia.)

### Treatment.

**A. Specific Measures** Hyperimmune vaccinia gamma globulin shows promise experimentally.

**B. General Measures** Penicillin has a generally favorable effect probably due to control of secondary bacterial invaders.

**C. Local Measures** Early in the disease provide good oral hygiene and apply petrolatum or mineral oil swabs to the nares. Gentle cleansing of the skin is advisable. If lesions are confluent and suppurating, treat as pyoderma. Treat itching with antipruritic lotions. restraints and sedation may be necessary.

**D. Treatment of Complications** Treat as indicated for secondary infections otherwise, treatment is symptomatic.

### Prognosis

The crusts usually disappear after 3 weeks. The severity of the illness and mortality depend upon the strain of virus. variola minor, 1% variola major, 20%. Modified smallpox is rarely fatal.

Downie, A. M., & A. Macdonald. Smallpox and related virus infections in man. Brit M Bull 8 191-5, 1953.

## VACCINIA

Vaccinia is the cutaneous and sometimes general reaction which occurs following the introduction of vaccinia virus in the course of immunization against smallpox. In normal circumstances it consists of a single local lesion at the site of inoculation which undergoes a characteristic evolution depending upon the state of immunity of the patient.

When no local reaction occurs following inoculation, either the vaccine or the technique is at fault. This is not due to immunity.

### Types of Vaccinia

**A. Primary Vaccinia.** In nonimmune inoculated patients a papule will appear on the third or fourth day, followed on the next day by an umbilicated vesicle which, in the course of 3-4 days, is surrounded by an erythematous area as pustulation occurs. The pustule dries to form a crust by about the twelfth day. The crust detaches in the ensuing week to leave the characteristic pitted vaccination scar.

Fever and malaise may appear on about the sixth day and persist for 1-2 days. Axillary adenopathy may be present. Viremia occurs regularly, and the virus may be isolated from throat secretions.

**B. Accelerated (Vaccinoid) Reaction** In subjects with partial immunity the course of vaccinia is accelerated and less severe, reaching a peak on the fifth to eighth days.

**C. Immune Reaction:** In subjects possessing a high degree of immunity, local erythema appears in 1-2 days. The papule which appears on the third day does not proceed to vesiculation or pustulation. This must be distinguished from transient local allergic reaction to the vaccine.

#### Complications.

**A. Autoinoculation** may result in one or more satellite lesions around the vaccination site or distant lesions elsewhere (including the conjunctivas).

**B. Generalized Vaccinia:** Generalized vaccinoid lesions may occur a few days after vaccination.

**C. Eczema vaccinatum** occurs in persons with generalized dermatoses who themselves are vaccinated or who are exposed to someone with vaccinia. The eruption becomes generalized, particularly in the area of dermatosis, it is associated with high fever and the manifestations of severe systemic disease, and may be fatal. It must be distinguished from generalized herpes simplex infection in persons with dermatoses (Kaposi's varicelliform eruption).

**D. Secondary infection of the lesion due to streptococci, staphylococci, or, rarely, Clostridium tetani** may occur

**E. Postvaccinal Rashes:** Scarlatiniform or rubelliform rash, erythema multiforme, and gangrene of lesions may occur

**F. Postvaccinal encephalitis**, manifested by sensorial alterations, meningeal irritation, and various abnormal neurologic findings, may appear 10-14 days after vaccination. Death may occur. Residua are not common

#### Treatment

No treatment nor dressing is required for uncomplicated vaccinia. Secondary infection may be treated with hot compresses and antibiotic ointment or systemic chemotherapy. Generalized vaccinia and eczema vaccinatum should be treated with vaccinia immune globulin, 1 ml./Kg. I.M. No specific treatment is available for postvaccinal encephalitis.

Kempe, C.H., & A.S. Benenson: Smallpox and vaccinia. P.Clin.North America 2:19-32, 1955.

## EPIDEMIC PAROTITIS (Mumps)

#### Essentials of Diagnosis.

- Painful, swollen salivary glands, usually parotid.
- Orchitis, meningoencephalitis, pancreatitis, CSF lymphocytic pleocytosis in meningoencephalitis.
- Exposure 14-21 days previously.

Nearby lymph gland disease, as in adenitis and infectious mononucleosis, must be differentiated from salivary gland involvement. Other causes of salivary gland involvement such as septic parotitis (usually in severely ill or debilitated patients) and salivary duct stone or stricture must also be distinguished. Mumps meningitis with minimal or no salivary gland involvement may be confused with other types of meningitis.

#### General Considerations.

Mumps is a viral disease spread by respiratory droplets which usually produces inflammation of the salivary glands and, less commonly, orchitis, meningoencephalitis, pancreatitis, and oophoritis. Most patients are children. The incubation period is 14-21 days (average 18 days). Infectivity precedes the symptoms by about 1 day, is maximal for 3 days, and then declines until the swelling has disappeared

#### Clinical Findings.

**A. Symptoms and Signs:** Fever and malaise are variable but are often minimal in young children. High fever usually accompanied orchitis or meningoencephalitis. Pain and swelling of one or both (75%) of the parotid or other salivary glands occurs, usually in succession 1-3 days apart. Occasionally one gland subsides completely (usually in 7 days or less) before others become involved. Pain and swelling of the testicle (orchitis) occurs in 25% of adult males with mumps. Headache and lethargy suggest meningoencephalitis. Upper abdominal pain, nausea, and vomiting suggest pancreatitis. Lower abdominal pain in females suggests oophoritis.

Parotid swelling is the commonest physical finding. Tenderness is usually present. Edema is occasionally marked. Swelling and tenderness of the submaxillary and sublingual glands is variable. The orifice of Stensen's duct may be reddened and swollen. Neck

stiffness and other signs of meningeal irritation are commonly present in meningoencephalitis. Testicular swelling and tenderness (unilateral in 75%) denote orchitis. Epigastric tenderness may be observed in pancreatitis. Lower abdominal tenderness and ovarian enlargement may be noted in mumps oophoritis but the diagnosis is often difficult.

**B Laboratory Findings** Relative lymphocytosis may be present although the blood picture is not of great diagnostic assistance. Serum amylase is commonly elevated with or without pancreatitis. Lymphocytic pleocytosis of the CSF is present in meningoencephalitis. Complement-fixing and chick cell agglutination inhibiting antibodies appear about 2 weeks after the onset of the disease.

### Complications

The complications of mumps are simply other manifestations of the disease less common than inflammation of the salivary glands. These usually follow the parotitis but may precede it or occur without salivary gland involvement: meningoencephalitis (30%), orchitis (25% of adult males), pancreatitis, oophoritis, thyroiditis, neuritis and myocarditis.

### Prevention

**A Mumps convalescent serum** 20 ml 1 M may reduce incidence in exposed susceptible

**B Mumps virus vaccine** may produce temporary active immunity. Intradermal injection of virus antigen denotes immunity if followed by local erythema.

### Treatment

**A General Measures** Isolate the patient until swelling subsides and keep at bed rest during the febrile period. Give aspirin or codeine for analgesia as required and alkaline aromatic solution mouth washes. Mumps convalescent serum, 20 ml or mumps convalescent gamma globulin 2.5 ml 1 M may reduce the incidence of orchitis in adult males.

### B Treatment of Complications

- 1 Meningoencephalitis (may be asymptomatic) - Give analgesics as necessary and do lumbar puncture if necessary to reduce headache. If symptoms are very severe hydrocortisone as for orchitis may be used.
- 2 Orchitis - Suspend the scrotum in a suspensory or towel bridge and apply ice bags. Incision of the tunica may be neces-

sary in severe cases. Give codeine or morphine as necessary for pain. Pain can also be relieved by injection of the spermatic cord at the external inguinal ring with 10-20 ml of 1% procaine solution. The inflammatory reaction should be reduced with hydrocortisone 100 mg I.V. followed by 20 mg orally every 6 hours for 2-3 days.

**3 Pancreatitis** Symptomatic relief only and parenteral fluids if necessary.

**4 Oophoritis** - Symptomatic treatment only.

### Prognosis

The entire course of the infection rarely exceeds 2 weeks. Fatalities (due to encephalitis) are very rare.

Habel K & J P Utz. Mumps. P Clin North America 7 979 88 1960

## POLIOMYELITIS

### Essentials of Diagnosis

- Muscle weakness, headache, stiff neck, fever, nausea, vomiting, sore throat.
- Lower motor neuron lesion (flaccid paralysis) with decreased deep tendon reflexes and muscle wasting.
- CSF shows excess cells. Lymphocytes predominate rarely more than 500/cu mm.

Abortive poliomyelitis may simulate acute respiratory infection or gastroenteritis and is usually not dangerous. Nonparalytic poliomyelitis is difficult to distinguish from other aseptic meningitides (encephalitis, mumps, Coxsackie virus infection, choriomeningitis), meningismus and granulomatous meningitis. Paralytic poliomyelitis may be mimicked by hysteria especially during outbreaks; hysterical paralysis may also occur with viral meningitis or other CNS disorders.

### General Considerations

The mode of transmission of poliomyelitis is not entirely known. The virus is present in throat washings and stools and infection probably can be acquired by the respiratory droplet route or by ingestion. Originally a disease of young children, the incidence has increased among older children and adults below the age of 40 years in areas where the

sanitary standards are high. Over 90% of infections are inapparent and result in immunity. Three antigenically different strains of poliomyelitis virus are known. The incidence of the disease is greatest during the summer months.

The incubation period is 5-35 days (usually 7-14 days). Infectivity is maximal during the first week, but excretion of virus in the stools may continue for several weeks. The family or other contacts of diagnosed cases may be "transient carriers" and secrete virus in the absence of symptoms or during the abortive type of infection.

## Clinical Findings

### A. Symptoms and Signs

1. Abortive poliomyelitis - The symptoms are fever, headache, vomiting, diarrhea, constipation, and sore throat.

2. Nonparalytic poliomyelitis - Symptoms of CNS invasion may appear during the prodromal illness or may occur after a brief symptom-free period or the initial symptoms may be those of neurologic involvement. Headache, pain in the neck, back and extremities, fever, vomiting, abdominal pain, lethargy, and irritability are present. Muscle spasm - spontaneous shortening of the muscle or hyperactive stretch reflex with limitation of extension by pain and contraction - is always present in the extensors of the neck and back, usually present in the hamstring muscles, and variably present in other muscles. Resistance to flexion of the neck is noted after a varying range of free flexion. The patient assumes the "tripod" position upon sitting up, which he usually does by rolling to avoid flexing the back. Straight-leg raising is less than 90°. Spasm may be observed when the patient is at rest or may be elicited by putting each muscle through the maximum range of motion. The muscle may be tender to palpation.

3. Paralytic poliomyelitis - Paralysis may occur at any time during the febrile period. In addition to the symptoms of nonparalytic poliomyelitis, tremors and muscle weakness appear. Paresthesias and urinary retention are noted occasionally. Constipation and abdominal distention (ileus) are common. Paralytic poliomyelitis may be divided into 2 forms which may coexist: (1) spinal poliomyelitis, with weakness of the muscles supplied by the spinal nerves, and (2) bulbar poliomyelitis, with weakness of the muscles supplied by the cranial nerves and variable "encephalitis" symptoms. Bulbar symptoms include diplopia (uncommon), weakness of mastication, facial weakness, dysphagia, dys-

phonia, nasal voice, regurgitation of fluids through the nose, weakness of the sternocleidomastoid and trapezius muscles, difficulty in chewing, inability to swallow or expect saliva and respiratory tract secretions.

Muscle spasm is present as in nonparalytic cases but does not involve completely motor-denervated muscles. Early spasm is often followed by contractures of paralyzed muscles. The two separate causes of pain are often confused. Spasm may appear in the opponent of paralyzed muscles or in partly weakened muscles. The paralysis is often preceded by coarse tremors and fasciculation of muscles. Paralysis is usually asymmetric. It is of the flaccid lower motor neuron type, and may be partial or complete. Paralysis of the neck flexors is manifested by "neck drop" on lifting the shoulders from the bed. Paralysis of the shoulder girdle often precedes intercostal and diaphragmatic paralysis. Partial paralysis of the rectus abdomini is manifested by deviation of the umbilicus on active flexion of the neck. Weakness of the intercostal muscles and diaphragm is demonstrated by diminished chest expansion, "rocking horse" respiration with paradoxical movement of the diaphragm, use of accessory muscles, and decreased vital capacity. Cyanosis and stridor may appear later due to hypoxia. Paralysis may quickly become maximal or may progress over a period of several days until the temperature becomes normal.

Deep tendon reflexes are diminished or lost, often asymmetrically, in areas of involvement.

In bulbar poliomyelitis there may be strabismus (rare), facial asymmetry, deviation of jaw on opening, loss of gag reflex, loss of movement of palate and pharyngeal muscles, pooling of secretions in the oropharynx, deviation of tongue, and loss of movement of the vocal cords. In bulbar respiratory involvement the respirations are dysrhythmic (varying in rate, rhythm, and depth). The patient can usually take deep breaths on command.

Lethargy or coma may be due to encephalitis or hypoxia. Such disturbances of consciousness are most often due to hypoventilation.

Hypertension, hypotension, and tachycardia may occur. Convulsions are rare.

B. Laboratory Findings The WBC is not characteristic. The sedimentation rate may be normal or mildly elevated. CSF pressure is normal or slightly increased, protein normal or slightly increased, glucose not decreased, cells usually less than 500 per cu. mm. (polymorphonuclears may predominate

early, lymphocytes later). CSF is normal in 5% of patients. The virus may be recovered from throat washings (early) and stools (early and late). Neutralizing and complement-fixing antibodies appear during or after the second week.

#### Complications.

Urinary tract infection, atelectasis, pneumonia, myocarditis, and pulmonary edema may occur. Late complications include cor pulmonale, osteoporosis, and urolithiasis.

#### Prevention

Note: Specific immunization schedules are given on p. 655.

Both inactivated poliomyelitis vaccine (IPV, Salk) and oral vaccine (live virus, Sabin) are licensed by the Food & Drug Administration for use in immunization. The effectiveness of IPV has been demonstrated by the steady decline of incidence of the disease from approximately 14,000 paralytic cases in 1955 to approximately 1000 in 1961. The issue of duration of immunity following infection has not been settled, but the presumption of lifelong protection following infection has favored development of a live but attenuated virus vaccine. The latter also has the advantage of being administered orally.

After extensive and apparently uneventful use of millions of doses of live virus vaccine in other areas, the vaccine was licensed for distribution in the U S A as follows: Type I on August 17, 1961, type II on October 10, 1961, type III on March 27, 1962. After a total of about 43 million doses given experimentally and after licensure, occasional instances of paralytic disease occurred within the presumptive incubation period of 30 days. After careful analysis by the Poliomyelitis Surveillance Unit of the United States Public Health Service and review by the Special Oral Poliomyelitis Vaccine Advisory Committee, it was concluded that patients had illnesses compatible with infection by the vaccine virus as follows: Type I, one case; type II, none; type III, 11 cases.\*

In an effort to wipe out poliomyelitis, public health authorities now recommend almost universal use of oral vaccine, regardless of

prior immunization with IPV. Routine immunization with oral vaccine, assuming development of a thoroughly safe type III strain, will probably eradicate "wild virus" in areas where the infection is still endemic. Live virus vaccine has the advantage of being communicable and tends to spread immunity even to those who do not participate in vaccination programs.

For information concerning dosage forms, storage, methods of administration, and use in mass vaccination programs, reference should be made to the brochures provided by pharmaceutical manufacturers or to public health agencies.

Because poliomyelitis is indistinguishable from other viral infections of the nervous system, symptoms of meningeal irritation warrant a regimen of rest and close observation, especially during the febrile period.

#### Treatment.

**A Early Phase** The patient should avoid travel, activity, and psychic stress, and should be spared unnecessary examinations. Perform a brief and cursory muscle check not more than once daily in acute cases. Muscle examination should not require vigorous muscular activity on the part of the patient. Maintain comfortable but changing positions in a "polio bed": firm mattress, foot board, sponge rubber pads or rolls, sandbags, and light splints. Give aspirin or aspirin combined with amphetamine and phenobarbital for pain and anxiety. Do not give opiates and barbiturates in sedative doses. Tranquilizers should be used with caution.

Hot wool packs (Kenny) or hydrocollator pads may be applied to the extremities or other areas for the relief of pain during the febrile period, but complete body packs should be used only when the patient is afebrile. Change of position, extremity packs, and analgesic drugs usually suffice to control muscle spasm. Depot forms of tubocurarine may be used with caution.

Dehydration and intestinal hypoactivity often lead to fecal impaction. Examine the patient frequently and give sufficient fluids to prevent this. Use enemas and neostigmine 1 M. if necessary.

\*Terry, L. L.: The Association of Cases of Poliomyelitis With the Use of Type III Oral Poliomyelitis Vaccines. A Technical Report, United States Department of Health, Education, & Welfare, September 20, 1962. Dr. Terry concludes that use of type III vaccine should be limited "to preschool and school age children and to adults at high risk, i.e., those travel-

ing to hyperendemic areas and those living in areas where type III epidemics... are present or impending." This recommendation is based largely on the fact that individuals whose illnesses were compatible with vaccine etiology were all age 16-52, all but 2 being 23 years of age or older.

Bladder weakness may occur with paralysis involving any muscle group, most commonly with paraplegia. If this happens, insert a Foley catheter with great aseptic care and connect it with a gravity bottle by means of a sterile clear plastic tube. Change the catheter every 5 days and remove it as soon as possible. Do not attempt chemoprophylaxis with antimicrobials. Treat specific urinary infection after removal of the catheter (or if fever and rigor occur), and only after identification of the organism and sensitivity tests.

During the early phase and as long as the patient is bedfast, give a neutral ash diet with a maximum of 0.5 Gm. calcium content daily (no milk or milk products), and maintain fluid intake to ensure an adequate daily output of low specific gravity urine (1.5-2 L. /day for adults). If nasogastric feedings are necessary, use liquid meat baby foods, juices, low-calcium soybean milk substitutes, lactose, and vitamins.

## B. Severe Cases

1 Mobilization of personnel and equipment - Symptoms of grave poliomyelitis require emergency mobilization of a medical-surgical team and basic equipment: tank respirator, preferably with a positive pressure attachment, tracheostomy surgical set, J. V. set (with polyethylene catheter and cut-down instruments) and aspirating pump

2. Indications for tracheostomy - Tracheostomy is indicated for airway impairment due to accumulated secretions, vocal cord paralysis or spasm (note: cyanosis, deep unconsciousness, and convulsions should not be permitted to occur), pharyngeal paralysis (impaired swallowing mechanism, regurgitation of food through the nose, aspiration of food-stuffs), rapidly falling vital capacity, high fever, or rapid extension of paralysis. If bronchoscopic examination is performed, tracheostomy should be done with the bronchoscope in situ

It is always advisable to place a nasogastric tube and to evacuate the stomach before tracheostomy. In most instances the tube should be left in place during the first few days of illness to prevent gastric distention and aspiration of stomach contents, and, when the patient's condition permits, to allow feeding of liquid formulas (see diet suggestions under Treatment, Early Phase, above).

Artificial respiration is usually necessary during tracheostomy, provide by means of oxygen-anesthesia bag, hand resuscitator, or clinical resuscitators, e.g., positive pressure devices. Note: Early tracheostomy may be lifesaving and may limit extension of disease

by preventing hypoxia. Indications must be more liberally construed with less experienced therapeutic teams. With an extremely skilled nursing staff tracheostomy may be avoided, but the risk of surgery is negligible in comparison with its lifesaving advantages. Use a transverse incision at the level of the cricoid with the neck extended. Insert the tube through first tracheal ring below cricoid. Never perform low tracheostomy in poliomyelitis, and never incise the cricoid.

3 Indications for respirator - A body respirator should be used in the following circumstances (1) For obvious respiratory inadequacy, fatigue, diminished respiratory excursion, anxiety, and tachycardia. (2) When the vital capacity is below 50% of normal. When vital capacity is 35% of normal, the use of a respirator is mandatory. (3) Children incapable of cooperating require expert clinical judgment but it is better to err in the direction of safety. Fatigue, tachycardia, disturbance of breathing pattern, or lethargy warrant a trial in a respirator.

4 Care of respirator patient with tracheostomy - Use separate urethral type nasoroal and open-ended bronchial catheters. Set the aspirator for maximum pressure of -10 inches of mercury (check gauge often with tube pinched off). Place a Y tube between the pump tubing and the catheter. Introduce the catheter with the Y open, close the open end during aspiration and withdrawal. Enter the right main stem bronchus by turning the head to the left and vice versa. Catheters and hands must be kept clean. Keep catheters in benzalkonium chloride, 1:20,000 solution, or 5% sodium bicarbonate solution (unboiled), prepared fresh daily. Do not dry the catheter before reintroducing it into the bronchi.

Rotate respirator carriage at least every 2 hours. Use the Trendelenburg position sparingly. Turn the patient manually on the respirator tray at least every half hour to prevent decubitus ulcers.

While the tracheostomy tube is open, supply aerosolized air or an oxygen stream, using a nebulizer in the circuit and attaching an open T tube to the tracheostomy tube adaptor or connecting it with a positive-pressure attachment if used. Mucosal drying can best be avoided by aerosol delivered at body temperature.

Obtain expert consultation at centers experienced with the care of respiratory paralysis. The technic is complex. Patients react strongly to lack of confidence of those in charge.

In patients with respiratory dysrhythmia (central paralysis), utilize combined endotracheal positive pressure synchronously with

the tank to maintain adequate tidal volume. In desperate cases give tubocurarine chloride 0.2-0.4 mg/Kg every 8-12 hours to induce relaxation of respiratory muscles.

For sleep use simple nondepressant sedatives preferably ethchlorvynol (Placidyl<sup>®</sup>). Do not give barbiturates.

For treatment or (rarely) chemoprophylaxis of respiratory tract infections use penicillin or erythromycin. Avoid broad-spectrum antibiotics to prevent the development of resistant urinary and respiratory tract infections.

Maintain tidal air required for patient's respiratory rate and weight. (See E. P. Radford Jr. & others: Clinical use of a nomogram to estimate proper ventilation during artificial respiration. *New England J Med* 251:877, 1954.) Avoid respiratory alkalosis by control of tidal air and appropriate blood-alveolar air studies.

**C Convalescence and Rehabilitation** The principles are to prevent deformity, avoid exercise during the febrile period, and mobilize early, give range of motion exercise and change position frequently during the febrile period, provide early active exercise under skilled direction as soon as feasible. Early bracing and splinting for therapeutic purposes are required to activate the therapy program. Note: All available physical and occupational therapy services, individual and group psychology, social services, and the cooperation of all medical specialties may be required in the rehabilitation process.

#### D Treatment of Complications

1. Gastric distention - Relieve by nasogastric intubation and aspiration; replace lost electrolytes by I.V. route.

2. Gastric hemorrhage (uncommon but may be fatal) - Give whole blood transfusions if bleeding or a perforated Curling's ulcer is suspected. Surgery should be undertaken under positive pressure respiration if perforation is proved.

3. Bladder atony and infection - See p. 613.

4. Ileus and impaction - See p. 612.

5. Atelectasis - Prevent by aerosolization of the air stream, preferably with aerosol saturated with water vapor at body temperature; periodic deep breathing by increasing tank pressure briefly; or by special vacuum attachment, change of position and prevention of respiratory infection, as well as good tracheobronchial toilet. If atelectasis occurs, treat with positive-pressure aerosol therapy, bronchial dilators, wetting agents

and, if necessary, trypsin or pancreatic dornase. Bronchoscopy is usually ineffective unless inspissated secretions are present.

6. Mental changes - Psychosis (usually short-lived) with confusion, disorientation and hallucinations or delusions occurs in a small percentage of cases. Early psychic disturbances usually indicate hypoxia. Post-acute depression is common in severe disease. It subsides in 6-8 weeks with supportive psychologic care and can often be prevented by meticulous care to prevent psychic trauma.

7. Pregnancy - Pregnant women have a high susceptibility to poliomyelitis and often develop severe disease. Expectant care should be attempted until term. At or near term carry the patient through labor in a tank respirator and deliver on an open respirator under positive-pressure respiration with local block or do cesarean section. The mortality rate is negligible with a well-coordinated respiratory and obstetric program. Early in pregnancy spontaneous abortion may occur or surgical abortion may be necessary. Try to avoid surgical abortion until the end of the febrile period.

#### Prognosis

Paralysis may occur or progress during the febrile period (3-10 days). Diffuse mild weakness is more favorable for functional recovery than severe weakness of a few important muscles. Bulbar poliomyelitis (10-20%) is the most serious. The over-all mortality rate is 5-10%.

Miner, R. W. (editor). *Biology of Poliomyelitis*, Conference. Ann. New York Acad. Sci. 61:737-1064, 1955.

Spencer, W. A. *Treatment of Acute Poliomyelitis*, 3rd ed. Thomas, 1956.

#### PSITTACOSIS (Ornithosis)

#### Essentials of Diagnosis

- Fever, chills, malaise, prostration, cough, epistaxis, occasionally, rose spots and splenomegaly.
- Slightly delayed appearance of signs of pneumonitis.
- Isolation of virus or rising titer of complement-fixing antibodies.
- Contact with infected bird (psittacine pigeons, many others) 7-15 days previously.



Psittacosis can often be distinguished from other viral pneumonias only by a history of contact with an infected bird and demonstration of complement-fixing antibodies. Pulmonary infiltrates must be differentiated from those which occur in other acute pneumonias and tuberculosis. Rose spots and leukopenia must be differentiated from typhoid fever.

#### General Considerations.

Psittacosis is due to a large virus acquired from contact with birds (parrots, parakeets, pigeons, chickens, ducks and many others). Human-to-human spread is rare. The incubation period is 7-15 days

#### Clinical Findings

**A. Symptoms and Signs** The onset is usually rapid, with fever, chills, headache, backache, malaise, myalgia, epistaxis, dry cough, and prostration. Signs include those of pneumonitis, alteration of percussion note and breath sounds, and rales. Pulmonary findings may be absent early. Rose spots, splenomegaly, and meningismus are occasionally seen. Delirium, constipation or diarrhea, and abdominal distress may occur.

**B. Laboratory Findings** The WBC is normal or decreased, often with a shift to the left. Proteinuria is frequently present. The virus may be isolated from the blood and sputum by mouse inoculation. Complement-fixing antibodies appear during or after the second week. The rise in titer may be minimized or delayed by early chemotherapy.

**C. X-ray Findings** The x-ray findings in psittacosis are those of central pneumonia which later becomes widespread or migratory. Psittacosis is indistinguishable from other viral pneumonias by x-ray.

#### Complications.

Myocarditis, secondary bacterial pneumonia.

#### Treatment.

Treatment consists of giving tetracycline drugs or chloramphenicol, 0.5 Gm. every 6 hours orally or 0.5 Gm.  $\frac{1}{2}$  V every 12 hours for 10-14 days. Give oxygen and sedation as required.

#### Prognosis.

Psittacosis may vary from a mild respiratory infection (especially in children) to a severe, protracted illness unless treated. Mortality with treatment is very low.

Brainerd, H. Q fever and psittacosis. *P. Clin North America* 3, 68-72, 1955

## LYMPHOGRANULOMA VENEREUM

#### Essentials of Diagnosis.

- Evanescent herpetic or ulcerative genital lesion
- Lymph node enlargement, softening, and suppuration, with draining sinuses
- Proctitis and rectal stricture in females.
- Systemic, joint, eye, and CNS involvement may occur
- Positive Frei skin test and complement fixation test.
- Elevated serum globulin

The early lesion of lymphogranuloma venereum must be differentiated from the lesions of syphilis, herpes prostaticus, and chancroid, lymph node involvement must be distinguished from that due to lymphoma, tularemia, tuberculosis, plague, and neoplasm, rectal stricture must be differentiated from that due to neoplasm and ulcerative colitis.

#### General Considerations.

Lymphogranuloma venereum is an acute and chronic contagious venereal disease caused by a specific virus. After the genital lesion disappears the infection spreads to lymph channels and lymph nodes of the genital and rectal areas. The disease is acquired during intercourse or through contact with contaminated exudate from active lesions. The incubation period is 5-21 days. Inapparent infections and latent disease (as shown by skin testing) are not uncommon in promiscuous individuals.

#### Clinical Findings.

**A. Symptoms and Signs** In males the initial herpetic or ulcerative lesion (on the external genitalia) is evanescent and often goes unnoticed. Inguinal buboes appear 1-4 weeks after exposure, are often bilateral, and have a tendency to fuse, soften, and break down to form multiple draining sinuses with extensive scarring. Proctoscopic examination is important for diagnosis and in evaluating therapy. In the female the genital lymph drainage is to the anal and perirectal glands. Early anorectal manifestations are proctitis

with tenesmus and bloody purulent discharge late manifestations are chronic cicatrizing inflammation of the rectal and perirectal tissue. These changes lead to obstipation and rectal stricture and occasionally rectovaginal and perianal fistulae.

Systemic invasion may occur causing fever arthralgia arthritis a skin eruption conjunctivitis and iritis. Nervous system invasion causes headache and meningeal irritation.

**B Laboratory Findings** The intradermal skin test (Frei test) and the complement fixation test are positive but cross reaction with psittacosis virus takes place. Because both tests remain positive throughout life a positive reaction may reflect an old (healed) infection however high complement fixation titers usually imply current infection.

The serum globulin is often greatly elevated with an inversion of the albumin globulin ratio. A low titer false positive test for syphilis may be present.

### Complications

Lymphatic involvement and blocking may cause marked disfiguration of the external genitalia (elephantiasis) as well as extensive scarring. Rectal stricture resists treatment and may require colostomy.

### Treatment

**A Specific Therapy** The tetracyclines and chloramphenicol (Chloromycetin<sup>®</sup>) 0.25 Gm orally q.i.d. for 5-14 days are the antibiotics of choice. Sulfadiazine or sulfathiazole 1 Gm t.i.d. for 2-3 weeks or longer probably has no effect against the virus but is effective in preventing secondary complications.

**B Local and General Measures** Place the patient at bed rest apply warm compresses to buboes and give analgesics as necessary. Aspirate fluctuant nodes under aseptic conditions (see below). Note incision and drainage are to be avoided (to prevent lymphatic obstructions). Extensive plastic operations may be necessary in the chronic and rectal form of the disease. Rectal strictures should be treated by prolonged gentle dilatation although in extreme cases this may be impossible and colon shunting procedures may be necessary.

### Prognosis

Prompt early treatment will cure the disorder and prevent late complications. The longer treatment is delayed the more difficult it is to eradicate the infection and to reverse the

pathologic changes. There seems also to be a higher incidence of rectal carcinoma in persons with anorectal lymphogranuloma venereum.

## ENCEPHALITIS

### Essentials of Diagnosis

- Fever malaise stiff neck sore throat and nausea and vomiting progressing to stupor coma and convulsions.
- Signs of an upper motor neuron lesion (exaggerated deep tendon reflexes absent superficial reflexes pathologic reflexes spastic paralysis).
- CSF protein and pressure often increased with lymphocytic pleocytosis.

Mild forms of encephalitis must be differentiated from aseptic meningitis lymphocytic choriomeningitis and non paralytic poliomyelitis. Severe forms from cerebrovascular accidents brain tumors and brain abscess.

### General Considerations

Encephalitis is a pathologic designation which includes a variety of clinical entities several of which are of unknown etiology. Arthropod borne encephalitis (St. Louis Eastern and Western equine encephalomyelitis etc.) is of viral etiology and is transmitted by mosquitoes. Epidemic encephalitis (Von Economo) is of unknown etiology and was observed to occur at the time of the 1918 influenza epidemic. The postinfectious encephalides (measles varicella variola vaccinia) are of unknown etiology but may be due to the viral infection or sensitivity to the virus or some product of it. Mumps meningoencephalitis is due to mumps virus. Sporadic encephalitis of varying clinical manifestations of unknown etiology is also observed.

### Clinical Findings

**A Symptoms and Signs** The symptoms are fever malaise sore throat nausea and vomiting lethargy stupor coma and convulsions. Signs include stiff neck signs of meningeal irritation tremors convulsions cranial nerve palsies paralysis of extremities exaggerated deep reflexes absent superficial reflexes and pathologic reflexes.

**B Laboratory Findings** The WBC is variable. CSF pressure and protein content

are often increased, glucose normal, lymphocytic pleocytosis may be present (polymorphonuclears may predominate early in some forms)

### Complications

Bronchial pneumonia, urinary retention and infection, and decubitus ulcers may occur. Late sequelae are mental deterioration, parkinsonism, and epilepsy.

### Treatment

Repeated lumbar punctures may relieve symptoms. Prevention or early treatment of decubiti, pneumonia and urinary tract infections is important. Give anticonvulsants as needed.

### Prognosis

Varies widely with type

Hammon, W M. The viral encephalitides (in man). Ann New York Acad Sc 70:292-361, 1958

## LYMPHOCYTIC CHORIOMENINGITIS

### Essentials of Diagnosis

- Influenza like\* prodrome of fever, chills, malaise and cough followed by meningitis with associated stiff neck
- Kernig's sign, headache, nausea, vomiting and lethargy
- CSF: slight increase of protein, lymphocytic pleocytosis ( $500-1000/\text{cu mm}$ )
- Complement-fixing antibodies within 2 weeks

The influenza-like prodrome and latent period before the development of the meningitis helps distinguish this from other aseptic meningitides, meningismus and bacterial and granulomatous meningitis. A history of exposure to mice is an important diagnostic clue.

### General Considerations

Lymphocytic choriomeningitis is a viral infection of the CNS. The reservoir of infection is the infected house mouse, although naturally infected guinea pigs, monkeys, dogs and swine have been observed. The virus escapes from the infected animal by means of oronasal secretions, urine and feces with transmission to man probably through contaminated food and dust. The incubation period is not definitely known but is probably 8-13

days to the appearance of systemic manifestations and 15-21 days to the appearance of meningeal symptoms. The disease is not communicable from man to man. Complications are rare.

### Clinical Findings

**A Symptoms and Signs** The prodromal illness is characterized by fever, chills, headache, myalgia, cough and vomiting. The meningeal phase by headache, nausea and vomiting and lethargy. Signs of pneumonia are occasionally present during the prodromal phase. During the meningeal phase there may be neck and back stiffness and a positive Kernig sign (meningeal irritation). Severe meningoencephalitis may disturb deep tendon reflexes and may cause paralysis and anesthesia of the skin.

**B Laboratory Findings** Leukocytosis may be present. CSF lymphocytic pleocytosis (total count is often  $500-1000/\text{cu mm}$ ) may occur with slight increase in protein and normal glucose. Complement-fixing antibodies appear during or after the second week. The virus may be recovered from the blood and CSF by mouse inoculation.

### Treatment

Treat as for encephalitis

### Prognosis

The influenza like attack (prodrome) may terminate in recovery or meningeal symptoms may suddenly appear after a few days of remission. An attack is sometimes initiated by meningeal symptoms. Fatality is rare. The illness usually lasts 1-2 weeks although convalescence may be prolonged.

Maurer, F D. Lymphocytic choriomeningitis. J Nat Cancer Inst 20:887-70, 1958

## DENGUE

(Break-bone Fever, Dandy Fever)

### Essentials of Diagnosis

- Sudden onset of high fever, chills, severe aching headache, sore throat, prostration and depression
- Biphasic fever curve: initial phase 3-4 days, remission few hours to 2 days, second phase 1-2 days
- Rash: maculopapular, scarlatiniform, morbilliform or petechial on extremities to torso, occurring during remission or second phase
- Leukopenia

In the pre-eruptive stage dengue may be difficult to distinguish from influenza, malaria, measles, and yellow fever, but the eruption, its distribution, and the occurrence in an area and during a time when *Aedes* mosquitoes are abundant usually clarify the diagnosis.

#### General Considerations

Dengue is a viral disease transmitted by the bite of the *Aedes* mosquito. It occurs only in the active mosquito season (warm weather). The incubation period is 3-15 days (usually 5-8 days).

#### Clinical Findings

**A. Symptoms and Signs.** Dengue begins with a sudden onset of high fever, chills, and severe aching (breakbone) of the head, back, and extremities, accompanied by sore throat, prostration, and depression. There may be conjunctival redness and flushing or blotching of the skin. The initial febrile phase lasts 3-4 days, followed by a remission of a few hours to 2 days. The skin eruption appears in 80% of cases during the remission or during the second febrile phase, which lasts 1-2 days and is accompanied by similar but usually milder symptoms than in the first phase. The rash may be scarlatiniform, morbilliform, maculopapular, or petechial. It appears first on the dorsum of the hands and feet and spreads to the arms, legs, trunk, and neck, but rarely to the face. The rash lasts 2 hours to several days and may be followed by desquamation.

**B. Laboratory Findings.** Leukopenia is characteristic.

#### Complications

Depression, pneumonia, iritis, orchitis, and oophoritis are rare complications.

#### Prevention

Available prophylactic measures include control of mosquitoes by screening and DDT. Dengue vaccine shows promise experimentally.

#### Treatment

Give salicylates as required for discomfort. Permit gradual restoration of activity during prolonged convalescence.

#### Prognosis

Fatality is rare. Convalescence is slow.

Howan, L. C. Recent work on dengue fever. *M. J. Australia* 44:530-3, 1957.

## COLORADO TICK FEVER

#### Essentials of Diagnosis

- Fever, chills, myalgia, headache, prostration
- Leukopenia
- Second attack of fever after remission lasting 2-3 days
- Onset 3-6 days following tick bite

Colorado tick fever resembles dengue but can be distinguished by place of occurrence and absence of rash. Influenza, Rocky Mountain spotted fever, and other acute leukopenic fevers must also be differentiated.

#### General Considerations

Colorado tick fever is an acute viral infection transmitted by *Dermacentor andersoni* bites. The disease is limited to the western United States and is most prevalent during the tick season (March to July). The incubation period is 3-6 days.

#### Clinical Findings

**A. Symptoms and Signs.** The onset of fever (to 102-105°F) is abrupt, sometimes with chills. Severe myalgia, headache, photophobia, anorexia, nausea, and vomiting, and generalized weakness are prominent symptoms. There are no abnormal physical findings. Fever continues for 3 days, followed by a remission of 2-3 days, and then by a full recrudescence lasting 3-4 days. In an occasional case there may be one or three bouts of fever.

**B. Laboratory Findings.** Leukopenia (2000-3000/cu mm) with a shift to the left occurs. Viremia may be demonstrated by inoculation of blood into hamsters or suckling mice. Complement-fixing antibodies appear during the third week after onset.

#### Complications

Aseptic meningitis or encephalitis occurs rarely. Asthenia may follow.

#### Treatment

No specific treatment is available. Aspirin or codeine may be given for pain.

#### Prognosis

The disease is self-limited and almost invariably benign.

Eklund, C. M., Kohls, G. M., & J. M. Brennan. Distribution of Colorado tick fever and virus-carrying ticks. *J. A. M. A.* 157:335-7, 1955.

## RABIES (Hydrophobia)

### Essentials of Diagnosis.

- Paresthesia, hydrophobia, aerophobia, rage alternating with calm.
- Convulsions, paralysis thick tenacious saliva.
- History of animal bite

Fear of the disease may result in a hysterical state which may closely simulate rabies. Muscle spasm may cause confusion with tetanus.

### General Considerations.

Rabies is a viral disease of animals and man, transmitted by infected saliva which gains entry into the body by a bite or an open wound. In the United States, rabies in man is usually due to the bite of an infected dog, although cats, wolves, skunks, bats, and other warm-blooded animals may be the source of infection. There is no specific climatic, geographic, or racial incidence. The incubation period may range from 10 days to 2 years, but is usually 3-7 weeks. The virus travels in the nerves to the brain, multiplies there, and then migrates along the efferent nerves to the salivary glands.

### Clinical Findings.

**A. Symptoms and Signs** There is usually a history of animal bite. Pain appears at the site of the bite, followed by tingling. The skin is quite sensitive to changes of temperature, especially air currents. Periods of rage alternate with calm intervals. Attempts at drinking cause extremely painful laryngeal spasm so that the patient finally refuses to drink (hydrophobia). The patient is restless, and behaves in a peculiar manner. There is muscle spasm, laryngospasm, and extreme excitability. Convulsions occur, and blowing on the back of the patient's neck will often precipitate a convulsion. Large amounts of thick tenacious saliva are present.

**B. Laboratory Findings** Biting animals who are apparently well should be kept under observation. Sick or dead animals should be examined for rabies. The diagnosis of rabies in the brain of a rabid animal may be made rapidly by the fluorescent antibody technic.

### Treatment.

Treatment consists of absolute quiet and freedom from stimulation, sedation, as in

tetanus, for preventing convulsions. No specific measures are available.

### Prevention.

If possible, the animal should be kept under observation. The wound should either be cauterized with fuming nitric acid and the acid then neutralized with lime water, or thoroughly washed with green soap.

After a positive diagnosis of rabies or after a bite by a suspected animal if the animal cannot be observed or if the bite is on the head, give rabies vaccine (duck embryo), 1 ml. subcut. daily for 14 days. Rabies hyperimmune serum should be administered in addition to vaccine in facial or severe hand bites.

### Prognosis.

Once the symptoms have appeared, death inevitably occurs after 2-3 days as a result of cardiac or respiratory failure or generalized paralysis.

Koprowski, H. Rabies. P. Clin. North America 2:55-63, 1955

## YELLOW FEVER

### Essentials of Diagnosis

- Sudden onset of severe headache,aching in legs, and tachycardia. Later, bradycardia, hypotension, jaundice, hemorrhagic tendency ("coffee-ground" vomitus).
- Proteinuria, leukopenia, bilirubinemia, bilirubinuria.
- Endemic area

It may be difficult to distinguish yellow fever from leptospirosis and other jaundices on clinical evidence alone, although the short course and mildness of the jaundice in yellow fever allow for some differentiation.

### General Considerations.

Yellow fever is a viral infection transmitted by the Aedes and jungle mosquitoes. It is endemic to Africa and South America (tropical or subtropical) but epidemics have extended far into the temperate zone during warm seasons. The mosquito transmits the infection by first biting an individual having the disease and then biting a susceptible individual after the virus has incubated within the mosquito's body. The incubation period in man is 3-6 days.

**Clinical Findings****A Symptoms and Signs**

1 Mild form Symptoms are malaise headache fever retroorbital pain nausea and vomiting and photophobia Bradycardia may be present

2 Severe form Symptoms are as for the mild form with sudden onset severe pains throughout the body extreme prostration bleeding into the skin and from the mucous membranes (coffee ground vomitus) oliguria and jaundice Signs include tachycardia erythematous face and conjunctival redness during the congestive phase followed by a period of calm (on about the third day) with a normal temperature and bradycardia and then a toxemic stage with return of fever bradycardia hypotension jaundice hemorrhages (gastrointestinal tract bladder nose mouth subcutaneous) and later delirium

**B Laboratory Findings** Leukopenia occurs although it may not be present at the onset Proteinuria is present sometimes as high as 5-6 Gm/L and disappears completely with recovery With jaundice there is bilirubinuria and bilirubinemia The virus may be isolated from the blood by intracerebral mouse inoculation (first 3 days) Antibodies appear during and after the second week

**Prevention**

Control mosquitoes by adequate screening and use of DDT A vaccine is available for persons going into endemic areas

**Treatment**

Treatment consists of giving a liquid diet limiting food to high carbohydrate high protein liquids as tolerated I.V. glucose and saline as required analgesics and sedatives as required and saline enemas for obstipation

**Prognosis**

Mortality is high in the severe form with death occurring most commonly from the sixth to the ninth day In survivors the temperature returns to normal by the seventh to eighth day The prognosis in any individual case should be guarded at the onset since sudden changes for the worse are not uncommon Hiccups copious black vomitus melena and anuria are unfavorable signs

Burnet F.M. Yellow fever Chap 25 pp 331-7 in *Natural History of Infectious Disease* 3rd ed Cambridge Univ 1933

**Essentials of Diagnosis**

- Abrupt onset with fever chills malaise cough coryza and muscle aches
- Aching fever and prostration out of proportion to catarrhal symptoms
- Leukopenia

Differentiate from the prodrome of other infectious diseases (e.g. measles dengue lymphocytic choriomeningitis) and from other common upper respiratory infections

**General Considerations**

Influenza is transmitted by the respiratory route While sporadic cases occur epidemics and pandemics appear at varying intervals usually in the fall or winter The 3 antigenic types (A B and C) produce clinically indistinguishable infections The incubation period is 1-4 days

**Clinical Findings**

**A Symptoms and Signs** The onset is usually abrupt with fever chills malaise muscular aching subaternal soreness headache nasal stuffiness and occasionally nausea In severe infections the patient may be prostrated Fever lasts 1-7 days (usually 3-5) Coryza nonproductive cough and sore throat are present Signs include mild pharyngeal injection flushed face and conjunctival redness

**B Laboratory Findings** Leukopenia is common Proteinuria (due to fever) may be present The virus may be isolated from the throat washings by inoculation of chick embryo Complement fixing and chick cell hemagglutination inhibiting antibodies appear during or after the second week

**Complications**

Influenza causes necrosis of the respiratory epithelium which predisposes to secondary bacterial infections The most frequent complications are acute sinusitis otitis media purulent bronchitis and bronchiolitis bronchiectasis and pneumonia

The circulatory system is not usually involved but pericarditis myocarditis and thrombophlebitis sometimes occur

Pneumonia may be due to secondary invaders (often staphylococci) or to the influenza virus itself

### Prevention.

Polyvalent influenza virus vaccine, 1 ml. subcut., or 0.1-0.2 ml. intradermally, given twice (1-2 weeks apart), exerts moderate temporary protection. Immunity lasts a few months to one year.

### Treatment.

Bed rest to reduce complications is the most important consideration. Analgesics and a sedative cough mixture may be used. Antibiotics should be reserved for treatment of bacterial complications.

### Prognosis.

The duration of the uncomplicated illness is 1-7 days, and the prognosis is excellent. Purulent bronchiolitis and bronchiectasis may result in chronic pulmonary disease and fibrosis which persist throughout life. Most fatalities are due to bacterial pneumonia. In recent epidemics mortality has been low except in debilitated persons, especially those with severe heart disease.

Francis, T., Jr. • Influenza. *M. Clin North America* 43:1309-26, 1959.

## CAT-SCRATCH FEVER

### Essentials of Diagnosis

- A primary infected ulcer or papule-pustule at site of inoculation (50% of cases).
- Regional lymphadenopathy which often suppurates.
- History of scratch by cat at involved area.
- Positive intradermal test.

Differentiate lymph node enlargement from that occurring in tularemia, lymphomas, neoplasms, tuberculosis, and lymphogranuloma venereum.

### General Considerations.

Cat-scratch fever is an acute infectious disease presumably due to a virus transmitted passively by healthy cats, principally by scratching, although cases have been reported to follow skin pricks by a splinter or thorn. The disease is world-wide in distribution, and appears to be quite common. Children are affected more often than adults.

### Clinical Findings.

**A. Symptoms and Signs** A few days after the scratch, about one-half of cases develop a primary lesion at the site of inoculation. This primary lesion appears as an infected, scabbed ulcer or a papule with a central vesicle or pustule. One to 3 weeks later, symptoms of generalized infection appear (fever, malaise, headache) and the regional lymph nodes become enlarged without evidence of lymphangitis. The nodes may be tender and fixed with overlying inflammation, or non-tender discrete, and without evidence of surrounding inflammation. Suppuration may occur with the discharge of sterile pus.

**B Laboratory Findings** The sedimentation rate is elevated, the WBC is usually normal and the pus from the nodes is sterile. Intradermal skin testing with antigen prepared from lymph node pus is positive (tuberculin-like reaction) in the majority of cases.

### Complications.

Encephalitis occurs rarely. Macular or papular rashes and erythema nodosum are occasionally seen.

### Treatment.

Tetracycline or chloramphenicol may shorten the course of the disease.

### Prognosis.

The disease is benign and self-limiting. Spontaneous cure may take from 2 weeks to 2 years. Antibiotic therapy may shorten the course of the disease.

Prier, J. E. • Cat-scratch fever. *Ann New York Acad. Sc.* 70:650-67, 1958.

## INFECTIOUS MONONUCLEOSIS

### Essentials of Diagnosis.

- Fever, sore throat, malaise, lymphadenopathy.
- Frequently splenomegaly, occasionally maculopapular rash.
- Positive sheep cell agglutinins (over 1:100); lymphocytosis with abnormal lymphocytes.
- Hepatitis frequent, and occasionally myocarditis, neuritis, encephalitis.

The sore throat must be distinguished from viral and bacterial sore

throat, the hepatitis from that of infectious hepatitis (abnormal lymphocytes may also be present) the skin rash from that occurring in rubella secondary syphilis and scarlet fever the lymphadenopathy from the nodal enlargement in the lymphomas and toxoplasmosis the neurologic manifestations from those occurring in viral encephalitis and the uncommon secondary hypersplenic phenomena from primary blood dyscrasias

### General Considerations

Infectious mononucleosis is an acute infectious disease of unknown etiology probably due to a virus. It is universal in distribution and may occur at any age but usually occurs in people between ages 10 and 35. It may occur both in an epidemic form or as sporadic cases. Its mode of transmission is also unknown but the agent presumably is airborne. The incubation period is probably 5-15 days.

### Clinical Findings

**A Symptoms and Signs** Symptomatology is varied but the typical case is represented by fever discrete nonsuppurative slightly painful moderately enlarged lymph nodes especially those of the posterior cervical chain and in approximately one half of cases splenomegaly. Sore throat is often present and toxic symptoms (malaise anorexia and myalgia) occur frequently in the early phase of the illness. A macular to maculopapular or occasionally petechial rash occurs in less than 50% of cases. Exudative pharyngitis tonsillitis or gingivitis may also occur.

A common manifestation of infectious mononucleosis is hepatitis with hepatomegaly nausea anorexia and jaundice. CNS involvement with headache neck stiffness photophobia pains of neuritis and occasionally even Guillain-Barre syndrome pulmonary involvement with chest pain dyspnea and cough, and myocardial involvement with tachycardia and arrhythmias.

**B Laboratory Findings** Initially there is a granulocytopenia followed within one week by a lymphocytic leukocytosis. Many of these lymphocytes are larger than normal adult lymphocytes, stain more darkly, and frequently show vacuolization of the cytoplasm and nucleus.

The heterophil test (sheep cell agglutination test) is usually positive but may not become positive until late in the course of the disease (fourth week) or may be positive only transiently. A titer over 1:100 is significant.

The STS is falsely positive in less than 10% of cases.

In CNS involvement the CSF may show an increase of pressure abnormal lymphocytes and protein.

With myocardial involvement the ECG may show abnormal T waves and prolonged P-R intervals.

Liver function tests are commonly abnormal.

### Complications

These usually consist of secondary throat infections often streptococcal and (rarely) rupture of the spleen or hypersplenism.

### Treatment

**A General Measures** Place the patient at bed rest until afebrile and give symptomatic treatment with aspirin codeine and hot saline or 30% glucose throat irrigations or gargles 3 or 4 times daily. In severely ill patients symptomatic relief may be afforded by corticotropin (ACTH) or one of the cortisones.

**B Treatment of Complications** Hepatitis myocarditis or encephalitis are treated symptomatically. Rupture of the spleen requires emergency splenectomy. Frequent vigorous palpation of the spleen is unwise.

### Prognosis

In the uncomplicated case the fever disappears in 10 days the lymphadenopathy and splenomegaly in 4 weeks. In some cases the illness may linger for 2-3 months.

Death is uncommon when it does occur it is usually due to splenic rupture or hypersplenic phenomena (severe hemolytic anemia thrombocytopenia purpura or encephalitis).

There are usually no sequelae.

Hoagland, R. J. Infectious mononucleosis.  
Am J Med 13:158-71, 1952.

## EPIDEMIC NEUROMYASTHENIA

This is a prolonged and variable syndrome consisting of headache nausea and vomiting diarrhea myalgia depression disturbances of mentation and nuchal rigidity without other abnormal physical findings or CSF pleocytosis. It may occur in epidemics. Treatment is symptomatic.

Henderson, D. A., & A. Shelokov. Epidemic neuromyasthenia: clinical syndrome? New England J Med 260:757-64, 1959.



## COXSACKIE VIRUS INFECTIONS

Coxsackie virus infections cause several clinical syndromes. As with other enteroviruses, infections are most common during the summer. Two groups, A and B, are defined by their differing behavior after injection into suckling mice. There are 24 serotypes, but many of these have not been shown to cause disease.

### Clinical Findings.

**A. Symptoms and Signs** The 6 clinical syndromes associated with Coxsackie virus infection may be described briefly as follows

1. Summer gripe (Coxsackie A and B) - A febrile illness, principally of children, which lasts 1-4 days, minor symptoms and respiratory tract infection are often present.

2. Herpangina (Coxsackie A2, 4, 5, 6, 8, 10) - Sudden onset of fever, which may be as high as 40.6°C. (105°F), sometimes with febrile convulsions, headaches, myalgia, vomiting, and sore throat, characterized early by petechiae or papules which become shallow ulcers in about 3 days and then heal.

3. Epidemic pleurodynia (Coxsackie B1, 2, 3, 4, 5) - Sudden onset of recurrent pain in the area of diaphragmatic attachment (lower chest or upper abdomen), fever is often present during attacks of pain, headache, sore throat, malaise, nausea, tenderness, hyperesthesia, and muscle swelling of the involved area, orchitis, pleurisy, and aseptic meningitis may occur. Relapse may occur after recovery.

4. Aseptic meningitis (Coxsackie A7, 9, B1, 2, 3, 4, 5) - Fever, headache, nausea, vomiting, stiff neck, drowsiness, CSF lymphocytosis without chemical abnormalities, rarely, muscle paralysis. See also Viral Meningitis, p. 635.

5. Acute nonspecific pericarditis (Coxsackie B5) - Sudden onset of anterior chest pain often worse with inspiration and in the supine position, fever, myalgia, headache, pericardial friction rub appears early, pericardial effusion with paradoxical pulse. Increased venous pressure, increase in heart size may appear, ECG and x-ray evidence of pericarditis often present. One or more relapses may occur.

6. Myocarditis neonatorum (Coxsackie B3, 4) - Heart failure in the neonatal period. The role of Coxsackie virus infection in "idiopathic" myocarditis of older children and adults is not known.

**B Laboratory Findings** Routine laboratory studies shown no characteristic abnormalities. Neutralizing antibodies appear during convalescence. The virus may be isolated from throat washings or stools inoculated into suckling mice.

### Treatment & Prognosis.

Treatment is symptomatic. With the exception of myocarditis, all of the syndromes caused by Coxsackie viruses are benign and self-limited.

Kibrick, S. The role of Coxsackie and ECHO viruses in human disease. *M Clin North America* 43:1291-1308, 1959.

## ECHO VIRUS INFECTIONS

ECHO viruses are enteroviruses which produce several clinical syndromes, particularly in children. Infection is most common during the summer.

Twenty serotypes have been demonstrated. Types 4, 6, and 9 cause aseptic meningitis (see pp. 623 and 635), which may be associated with a rubelliform rash. Types 9 and 16 cause an exanthematous illness (Boston exanthem) characterized by a sudden onset of fever, nausea, and sore throat, and a rubelliform rash over the face and trunk which persists 1-10 days. Orchitis may occur. Type 18 causes epidemic diarrhoea, characterized by a sudden onset of fever and diarrhoea in infants. Types 18 and 20 cause summer gripe (see p. 117). There are no characteristic laboratory abnormalities.

Treatment is symptomatic and the prognosis is excellent. Paralysis has occurred in aseptic meningitis due to ECHO virus infection, but very rarely.

Sanford, J. P., & S. E. Sulkin. The clinical spectrum of ECHO-virus infection. *New England J. Med.* 261:1113-22, 1959.

## ADENOVIRUS INFECTIONS

Adenoviruses (there are at least 18 antigenic types) produce a variety of clinical syndromes. These infections are self-limited, and most common among military recruits,

although sporadic cases occur in civilian populations. The incubation period is 4-9 days.

There are 4 clinical types of adenovirus infection

(1) The common cold Many infections produce rhinitis, pharyngitis, and mild malaise without fever indistinguishable from the symptoms and signs of other infections which produce the common cold syndrome

(2) Acute undifferentiated respiratory disease, nonstreptococcal exudative pharyngitis Fever lasts 2-12 days (usually 5 days) accompanied by malaise and myalgia Sore throat is often manifested by diffuse injection, a patchy exudate, and cervical lymphadenopathy Cough is sometimes accompanied by rales and x-ray evidence of pneumonitis (primary atypical pneumonia) Conjunctivitis is often present.

(3) Pharyngoconjunctival fever Fever and malaise, conjunctivitis (often unilateral), and mild pharyngitis

(4) Epidemic keratoconjunctivitis (shipyard eye) Unilateral conjunctival redness mild pain and tearing with a large preauricular lymph node.

A polyvalent vaccine is available, but is not recommended for general civilian use.

Treatment is symptomatic

Parrott, R H , & H G Cramblett: Nonbacterial infections affecting the nasopharynx  
P. Clin North America 4 115-38, 1957

## HEMADSORPTION VIRUS INFECTIONS

Hemadsorption viruses have been incriminated as the cause of upper respiratory infections in children.

## RICKETTSIAL DISEASES (RICKETTSIOSES)

The rickettsioses are a group of febrile diseases caused by several species of rickettsiae, transmitted to man either directly by vector bites (mite- or tick-borne forms) or by inoculation of vector feces (insect-borne forms). The natural reservoir of the rickettsiae is the arthropods, in which they live apparently without causing disease. In man the organisms multiply rapidly, causing a focal perivascular infiltration with or without damage to the vascular walls.

Some forms of rickettsiosis are geographically localized, although 2 or more forms may coexist in the same region. Fever is of greatly varying severity, and is usually associated with an early onset of rash. A local primary lesion (eschar) is found at the site of the vector bite in rickettsialpox, scrub typhus and local forms of Old World tick typhus. Nonspecific proteus agglutinins (Well-Felix) appearing in the second or third week of the illness may be of value in differential diagnosis. Complement fixation tests are of most value in differentiating diseases of the typhus group. Recovery of the organisms from the blood, urine, and other body fluids is cumbersome and usually clinically impractical.

### Prevention

(1) Typhus (epidemic) vaccine (Cox type), 1 ml. subcut, twice at intervals of 7-10 days,

(2) Rocky Mountain spotted fever vaccine, 1 ml. subcut, 3 times at intervals of 5-7 days.

These 2 vaccines do not protect against other forms of typhus.

### Treatment.

Since all forms of rickettsiosis respond to tetracyclines and chloramphenicol, their treatment can be discussed collectively.

**A Specific Measures** Give either of the following (1) Tetracycline drugs, 0.5-1 Gm. orally every 6 hours for 2-7 days, or 0.5 Gm. 1 V every 12 hours (2) Chloramphenicol (Chloromycetin®), 0.5 Gm. orally every 6 hours for 2-7 days

**B General Measures** Give parenteral fluids, oxygen, sedation, and other supportive measures as needed. Delousing procedures must be carried out for louse-borne infections.

## LOUSE TYPHUS (Epidemic Typhus)

### Essentials of Diagnosis

- Nonspecific prodrome of "flu-like" symptoms, followed by abrupt onset of chills, fever, and prostration
- Rash (third to eighth day) maculopapular, becoming hemorrhagic, trunk to extremities, sparing face, scalp, palms and soles.
- Splenomegaly (one-third of cases)
- Confirmed by animal inoculation, complement fixation, or Well-Felix serologic test.

Before the characteristic rash appears it is impossible to diagnose typhus on clinical grounds alone, since the prodromes or early stages of many diseases are similar to the early stage of typhus. The rash usually clarifies the diagnosis, however, rash is absent in up to 10% of cases, and is difficult to recognize in dark-skinned races.

#### General Considerations.

Epidemic typhus is due to *R. prowazekii*, which is transmitted in the feces of the body louse. It occurs more commonly in cooler climates and seasons. It is frequently a severe disease, but many undetected cases occur in young people in hyperendemic areas. Brill's disease represents an exacerbation of the epidemic variety occurring long after the initial infection. The incubation period is 5-15 days (usually 8-12 days)

#### Clinical Findings.

A. Symptoms and Signs Prodromal symptoms of malaise, cough, nausea, coryza, headache, and chest pain may occur a few days before the actual onset. The onset is abrupt, with chills, fever, severe prostration, headache, nausea and vomiting, constipation or diarrhea, cough, chest pain (usually non-pleuritic), stupor, delirium, and muscle aching.

The face is flushed and the conjunctivas are reddened. Bassi rales are frequently present. The BP may be low. Splenomegaly occurs in one-third of cases. The rash is a characteristic feature, appearing from the third to the eighth day (usually the fifth). The lesions are pink maculopapules which often become hemorrhagic, beginning on the trunk and spreading to the extremities. The rash rarely involves the face, scalp, palms, or soles.

B. Laboratory Findings. The WBC is inconstant, leukopenia is usually present the first week, leukocytosis the second week. Proteinuria is common. Hematuria may be present. Rickettsiae may be isolated by inoculation of guinea pigs or chick embryos with blood. Proteus OX-19 and perhaps OX-2 agglutinins appear at the end of the first week or during the second week. Complement-fixing antibodies appear during or after the second week.

#### Complications.

Pneumonia, gangrene of the extremities, peripheral circulatory collapse, myocarditis, or parotitis may occur.

Prevention & Treatment See above.

#### Prognosis.

The duration of the fever is usually about 2 weeks. The mortality in louse-borne typhus has been 5-80% in different epidemics. Specific chemotherapy has reduced the mortality rate greatly.

Recrudescences occurring in people who have left endemic areas (Brill-Zinsser episodes) are discussed below under flea typhus, with which they are readily confused.

Wilcocks, C.: Typhus group of fevers. *Trop. Dis. Bull.* 55:1065-73, 1958.

### FLEA TYPHUS (Endemic Murine Typhus)

The distribution of flea typhus is wider than that of louse typhus and the disease occurs in warmer climates and during warmer seasons (summer and fall). The animal reservoir is rodents, especially house rats. Body lice may occasionally pick up *R. typhi* (*R. mooseri*) from a patient with flea typhus and transmit it to others, but such small outbreaks cannot usually be distinguished from infections in the same household through infected fleas.

Flea typhus resembles recrudescence louse typhus (Brill-Zinsser) more than the severe louse typhus. The onset is often more gradual, the duration is shorter (9-14 days), the rash and symptoms less marked and complications are unusual and rarely fatal. The centripetal and relatively less developed rash, avoiding the face, palms, and soles, distinguishes flea typhus from those forms of tick typhus (with centrifugal rash) which frequently occur in the same geographic areas.

OX-19 reaction is positive. Specific complement-fixing antibodies are detectable.

Prevention and treatment are discussed on p. 624.

About 10% of untreated cases are fatal.

Pratt, H.D.: The changing picture of murine typhus in the United States. *Ann. New York Acad. Med.* 70:516-27, 1958.

## TRENCH FEVER

Trench fever may be included in the typhus group in spite of the apparent distinctiveness of the fever and the atypical features of *R. quintana* (pediculi) infection. The incubation period is 14-30 days but some attacks are apparently recrudescences (long delayed relapses) as in Brill Zinsser episodes. Endemic areas probably exist mostly in Poland, Yugoslavia, the Ukraine and recently reported in Mexico. The vector is the body louse; the animal reservoir is probably man.

There is an abrupt primary febrile attack, often lasting about 5 days, relapses of fever (usually 3-5 days), regular or irregular occur in about half the cases following primary attack. Pain behind the eyes, in the back and in the shins may suggest dengue (due to several different viruses) or influenza. Splenic enlargement occurs (rare in dengue) and general lymphadenopathy is common. Other findings are headache and nystagmus. The rash consists of relatively scanty and transitory erythematous macules or maculopapules fading on pressure, appearing early but irregularly during the primary attack or a relapse, particularly noticeable on the chest, back and abdomen. Latent infections and blood carrier states are well recognized.

The Weil-Felix reaction is negative. Specific complement fixing antibodies have been reported. Proteinuria is present often with polyuria.

Prevention and treatment are discussed on p. 624.

The prognosis is good but convalescence from this relatively mild fever is often protracted with vague functional disorders, somewhat resembling those which accompany the post-febrile depression of dengue and influenza.

Gal Perin, E. A. Rickettsiosis quintana (five day fever): its pathogenesis, clinical features and diagnosis. [Translated from Russian.] *J. Microbiol. Epidemiol. & Immunobiol.* 28: 835-7, 1957.

## TICK TYPHUS

(Rocky Mountain Spotted Fever, Boutonneuse Fever, North Queensland Tick Typhus, Etc.)

The tick-borne rickettsioses or spotted fevers are essentially similar but exist in

geographically and ecologically localized forms which have received local names. Usually rural in distribution, these local forms of tick typhus and their causative rickettsiae are associated with a few local species of hard ticks, mostly of the genera *Dermacentor*, *Haemaphysalis*, *Amblyomma* and *Rhipicephalus* and their local animal hosts (rodents, rabbits and dogs). The causative organisms of all may be regarded as subspecies of *R. rickettsii*.

There appear to be 3 major forms of tick typhus: (1) American type (subsp. *R. rickettsii*) characterized by absence of an eschar and typified by Rocky Mountain spotted fever, extending in patches from Canada to Brazil and westward into the U.S.S.R. (where it may be confused with *R. sibirica*) and India and presumably into parts of China. (2) African type (subsp. or sp. *R. conorii*), typified by boutonneuse fever, extending in patches over Africa, the Mediterranean region and into the U.S.S.R. and India. It is characterized by the frequent presence of an eschar (tache noir of Mediterranean region). In the Mediterranean region (and possibly parts of India) this is transmitted by *Rhipicephalus sanguineus* and therefore tends to be concentrated around urban areas (e.g., eastern parts of the United States). Elsewhere infections are in rural areas. (3) Australian type (subsp. or sp. *R. australis*), typified by North Queensland tick typhus, a mild infection apparently transmitted by a tick (probably *Ixodes*), resembles the African type in that an eschar is present but the organism is antigenically distinct.

See Rivers & Horsfall in Bibliography, p. 629.

## 1. ROCKY MOUNTAIN SPOTTED FEVER

## Essentials of Diagnosis

- Nonspecific flu-like prodrome followed by chills, fever, malaise, muscle and joint pains, restlessness and irritability.
- Splenomegaly (50%); occasional hepatomegaly and jaundice.
- Rash: red macular becoming larger and petechial on wrists, ankles and back, spreading to trunk.
- Serologic tests and animal inoculation confirm the diagnosis.

The early clinical course of Rocky Mountain spotted fever may resemble

the early clinical course of many infectious diseases, but the appearance, distribution, and march of the rash distinguish it from measles, typhus, and typhoid fever (rose spots). The rash of meningococcal meningitis may, however, simulate that of Rocky Mountain spotted fever, in which case blood culture and lumbar puncture may be necessary.

#### General Considerations.

Rocky Mountain spotted fever, due to *Rickettsia r. rickettsii*, is transmitted by various species of ixodid ticks. The disease occurs throughout the United States, although it is commonest in the Rocky Mountain and south-eastern areas. The majority of cases occur in late spring or early summer. The incubation period is usually 3-7 days.

#### Clinical Findings.

A. Symptoms and Signs. Prodromal malaise and anorexia may appear 1-3 days before the onset of chills or chilly sensations, sweating, fever, malaise, headache, retroorbital pain, photophobia, epistaxis, arthralgia, myalgia, nausea and vomiting, sore throat, and abdominal pain. Restlessness irritability, delirium, lethargy, stupor, or coma may appear. There may be a dusky flush of the face, conjunctival redness, cyanosis, splenomegaly (50%), and occasionally hepatomegaly or jaundice. A rash appears from the second to the eleventh day (usually the third to fifth), first on the wrists and ankles and then spreading to the trunk and extremities, and occasionally to the face. The rash spreads for 2-3 days. The eruption is initially small, red, and macular, then becoming larger and petechial.

B. Laboratory Findings. Proteinuria, bilirubinuria, and hematuria may be present. *Rickettsiae* can be isolated by intraperitoneal inoculation of male guinea pigs with citrated whole blood or serum. The Weil-Felix agglutination titer (OX-19 and OX-2) rises between the tenth and fifteenth days. It should be compared with an "acute" specimen taken during the first week. Complement-fixing antibodies appear during the second week.

#### Complications.

Myocarditis, bronchial pneumonia, skin necrosis, or cerebral infarction may occur.

Prevention & Treatment. See p. 624.

#### Prognosis.

The fever usually persists 2-3 weeks (convalescence is prolonged). Mortality before treatment with tetracycline drugs or chloramphenicol was 25-75%.

## 2. OTHER FORMS OF TICK TYPHUS

African tick typhus is generally mild, usually terminating by rapid lysis in the second week. An abrupt onset is usual, with severe headache, some insomnia and photophobia, myalgia, and arthralgia. Constipation and mental disturbance is not marked. In a varying proportion of cases, an eschar is already developed at onset, with painful enlargement of regional lymph nodes. The eschar may be anywhere on the body, at the site of the tick bite, but is usually on covered parts. The rash is similar to that of the American type, but is less often petechial and may be transitory or absent, especially outside the Mediterranean region. In the mildest cases, there may be no more than a few days of fever with headache, with or without an eschar and lymphadenopathy.

North Queensland tick typhus has been little studied. Fever lasts less than a week and may be intermittent. The rash is variable in character and may be fleeting.

## RICKETTSIALPOX

Rickettsialpox is due to *Rickettsia akari*, which is transmitted by mites from mouse reservoirs. The incubation period is 1-2 weeks. The disease is characterized by a sudden onset of chills, fever, myalgia, malaise, headache, and photophobia. The primary lesion is a firm red papule which becomes vesiculated and finally develops a black eschar. A papular eruption which becomes vesicopustular appears 2-4 days after the onset of symptoms. The vesicles crust in about 2 days, the crusts are shed in 1-2 weeks. Leukopenia is frequently found. Complement-fixing antibodies appear during or after the second week. The Weil-Felix reaction is negative.

Rickettsialpox must be differentiated from varicella, variola, flea typhus, Rocky Mountain spotted fever, and scrub typhus.

Treatment is discussed on p. 624.

Greenberg, M., & others Rickettsialpox - a newly recognized rickettsial disease II  
Clinical observations J A M A 133 901-6, 1947

### SCRUB TYPHUS (Tsutsugamushi Fever)

#### Essentials of Diagnosis

- Nonspecific flu-like prodrome
- Black scab or ulcerated eschar at site of inoculation often present
- Lymphadenopathy especially at site of eschar drainage
- Macular rash (one-third of cases) greatest on trunk
- Fever lasts 2 weeks and falls by lysis
- Serologic tests and animal inoculations confirm the diagnosis

Clinical differentiation of scrub typhus from other rickettsial infections typhoid fever malaria dengue infectious hepatitis and fever of unknown origin during the first week of the illness is difficult to impossible. The rash eschar and epidemiologic information aid in the diagnosis. The lymphadenopathy must be differentiated from other causes of lymph gland enlargement.

#### General Considerations

Scrub typhus is caused by *Rickettsia tsutsugamushi* which is transmitted by mites. It occurs in Japan southern Asia Indonesia and the southeast Pacific islands. The incubation period is 6-18 days (usually 10-12).

#### Clinical Findings

**A Symptoms and Signs** The prodrome (1-5 days) consists of malaise chills head ache backache retroorbital pain nausea and low-grade fever followed by a gradual or sudden increase of symptoms with high fever. A black eschar with necrotic center surrounded by erythema develops at the site of the primary inoculation. Regional adenopathy in the lymph channels draining the area of the ulcer occurs early, generalized adenopathy occurs at the peak of the disease. A macular rash appears on the third to eighth day in one-third of cases. It is maximal on the trunk, less intense on the extremities and occasionally appears on the face. The rash persists 1-8 days.

**B Laboratory Findings** A rising titer Weil-Felix reaction (proteus OXK) appears during or after the second week. Complement fixing antibodies appear during or after the second week. *Rickettsiae* can be isolated by intraperitoneal inoculation of white mice with whole blood.

#### Complications.

There may be myocarditis neuritis pneumonia or peripheral vascular collapse.

**Prevention & Treatment** See p 624

#### Prognosis

The fever usually persists 2 weeks. The mortality rate before specific treatment was available was 10-20%.

Wisseman C L., & others Studies on cortisone and antibiotics for prompt therapeutic control of typhoid fever and scrub typhus  
J Clin Invest 33 264 75, 1954

### Q FEVER

Q fever is caused by *Rickettsia (Coxiella) burnetii*. The mode of transmission is uncertain, but inhalation of dried material shed by livestock and drinking infected milk are probable mechanisms. The disease is transmitted by ticks in Australia. The incubation period is 2-4 weeks.

The disease is characterized by an abrupt onset with headache coryza cough myalgia retroorbital pain fever, and chills (often twice daily). There may be no physical signs but pulmonary rales and hepatomegaly are sometimes found. The Weil-Felix reaction is negative. *Rickettsiae* may be recovered by mouse inoculation with whole blood (dangerous). Complement-fixing antibodies appear during or after the second week. Pulmonary infiltration is seen on x-ray in 30% of cases. Complications include thrombophlebitis and hepatitis.

Q fever must be differentiated from influenza viral pneumonia amebic hepatitis and brucellosis.

For treatment see p 624

In young persons the illness usually lasts only a few days in older persons it may last many weeks. Fatalities are rare.

See reference under Psittacosis p 615

## Bibliography.

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## Infectious Diseases: Bacterial

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### STREPTOCOCCIC INFECTION OF THE UPPER RESPIRATORY TRACT, STREPTOCOCCIC PHARYNGITIS, SCARLET FEVER

#### Essentials of Diagnosis

- Abrupt onset of fever, malaise, sore throat, vomiting
- Throat red, edematous, with patchy or follicular exudate
- Finely papular erythematous rash appears promptly, especially in the axilla and groin
- Diagnosis confirmed by throat culture

The sore throat of streptococcal infection (with erythema, exudate, and edema) must be differentiated from viral and mycotic pharyngitis, diphtheria, Vincent's angina, and infectious mononucleosis. The rash of scarlet fever must be distinguished from the erythema and rash in rubella, toxic absorptive reaction, primary skin diseases, drug rash, and sunburn.

#### General Considerations

Streptococcal respiratory infections are caused by Lancefield group A beta-hemolytic streptococci. Transmission is primarily via respiratory droplets from patients with active disease or asymptomatic carriers. Scarlet fever occurs when the streptococcal strain is able to elaborate an erythrogenic toxin and in patients who are susceptible to the action of the toxin, and thus differs from streptococcal pharyngitis only by the appearance of a rash with strawberry tongue and other manifestations. The incubation period of streptococcal infection is 1-7 days.

#### Clinical Findings

**A Symptoms and Signs** Fever usually appears abruptly, accompanied by chills, or, in children, by convulsions. Malaise, arthralgia, nausea and vomiting, and abdominal pains

may occur and may be very severe. The throat is usually extremely sore and painful, although uncommonly the sore throat may be minimal and less striking than the other symptoms.

The local pharyngeal lesions are identical in streptococcal pharyngitis and scarlet fever. There is marked erythema and moderate edema of the pharynx with enlargement of the tonsils if they are present. A patchy or follicular purulent exudate which is easily removed is present on the tonsils, often on the posterior pharynx, and occasionally on the soft palate. The anterior cervical lymph nodes are tender and enlarged, and there is usually a slight generalized lymphadenopathy.

With the toxic manifestations (scarlet fever) the skin is diffusely erythematous with a punctate rash caused by enlarged skin papillae which are more deeply red than the surrounding skin. The rash is most intense in the axillae and groin and on the lateral trunk wall, the flexor surfaces of the arms, and the dorsum of the feet. It blanches on pressure. The extensor surfaces of the arms are usually spared. The skin folds are hyperpigmented and will not blanch on pressure. Small petechial hemorrhages may appear in the skin. The rash usually fades in 2-5 days and may be followed by a desquamation which begins with "pinholes" over the skin papillae. The face is usually flushed (with circumoral pallor) but is not involved by the rash. An enanthem - also due to the erythrogenic toxin - appears as a stippling of the soft palate analogous to the skin rash. The "strawberry tongue" begins to develop on the first day of exanthem. The tongue is heavily coated, prominent papillae are visible. The coat disappears at the tip and lateral margins on the second day, on the third day it is half to two-thirds gone, and on the fourth day the tongue is smooth and bright red, with enlarged papillae.

**B Laboratory Findings** Leukocytosis is present early, eosinophilia may appear during convalescence. The urine may show proteinuria, cylindruria, and hematuria. The sedi-



mentation rate is elevated and returns to normal during the second week in uncomplicated cases. The antistreptolysin O titer rises during convalescence. Beta-hemolytic streptococci may be cultured from the throat. During the first 2 days of the rash it may be blanched locally by the intradermal injection of 0.1 ml of antitoxin, although this test is rarely indicated. The blanching appears in about 12 hours.

### Complications

The bacterial complications include rhinitis, sinusitis, otitis, mastoiditis, suppurative cervical lymphadenitis, pneumonia and empyema (rare), suppurative arthritis, and meningitis. Rheumatic fever may occur after the second week, acute glomerulonephritis (with nephritogenic strains of streptococci) may occur in the third week or later.

### Differential Diagnosis

A. Streptococcal pharyngitis needs to be differentiated from the following: (1) Viral pharyngitis, especially herpangina and exudative nonbacterial pharyngitis. (2) Diphtheria, in which the throat is less red and the pseudomembrane is confluent. Systemic symptoms are less marked. (3) Vincent's angina with shallow ulcers usually involving the mouth. (4) Infectious mononucleosis, with more marked adenopathy, splenomegaly, abnormal lymphocytes and a positive heterophil test. (5) Pharyngomycosis, usually with dead-white patches of exudate and little erythema.

B. The rash of scarlet fever needs to be differentiated from the following: (1) Measles, distinguished by Koplik's spots and leukopenia. (2) Rubella, in which the fading rash may simulate scarlet fever, facial involvement is uncommon in scarlet fever. (3) Other erythemas (solar, drugs, febrile), usually differentiated on the basis of the history. (4) Prodromal rashes in varicella and variola (rare).

### Prevention

A. Scarlet fever toxin, in 5 weekly injections of 500, 2000, 8000, 25,000, and 80,000 units subcut., prevents the toxic manifestations of scarlet fever but does not prevent streptococcal infection.

B. Sulfonamides, 0.5 Gm ( $7\frac{1}{2}$  gr) b.i.d., penicillin G, 100,000 units by mouth b.i.d., or benzathine penicillin, 1,200,000 units I.M. once a month, reduce the incidence of streptococcal infection. These should be reserved for persons with rheumatic lesions to prevent recurrence of rheumatic fever.

### Treatment.

#### A. Specific Measures

1. Procaine penicillin G, 300,000 units daily I.M. Penicillin must be continued 10 days or relapse may occur. Oral penicillin, 200,000 units (or phenethicillin [Synclillin<sup>®</sup>], 250 mg) every 6 hours, or benzathine penicillin G (Bicillin<sup>®</sup>), 1,200,000 units I.M., may be used. Local penicillin by lozenges is worthless.

2. Erythromycin, 0.2-0.5 Gm every 6 hours, or tetracycline drugs, 0.25-0.5 Gm every 6 hours, is effective but may be followed by bacteriologic or clinical relapse.

3. Scarlet fever streptococcus antitoxin (9000-36,000 units) may be given I.M. with benefit in severely toxic cases of scarlet fever.

4. Convalescent serum, 25-150 ml, may be used similarly to antitoxin and may be given I.V.

B. General Measures. Place the patient at bed rest until he is afebrile and the sedimentation rate is normal. Modify the diet as necessary for sore throat. Hot saline or 30% glucose gargles or throat irrigations 3 or 4 times daily may be used for relief of sore throat. Give aspirin or codeine as necessary for symptomatic relief.

C. Treatment of Complications. Bacterial complications can usually be treated effectively with penicillin. Rheumatic fever may be prevented by early vigorous treatment of the infection with penicillin. Acute hemorrhagic glomerulonephritis is discussed in Chapter 26.

D. Treatment of Carriers. 300,000 units of penicillin procaine complex daily I.M. for 10 days, or benzathine penicillin G, 1,200,000 units I.M., usually abolishes the carrier state.

### Prognosis

In untreated, uncomplicated cases, fever persists 3-7 days and the rash begins to fade after 3-5 days. The course is shortened and complications minimized by early active treatment. Mortality is negligible.

Rammelkamp, C. H., Jr. Natural history of streptococcal infections. Bull. New York Acad. Med. 31:103-12, 1955.

Stillerman, M., & S. H. Bernstein. Streptococcal pharyngitis, evaluation of clinical syndromes in diagnosis. Am. J. Dis. Child. 107:475-89, 1961.

## DIPHTHERIA

### Essentials of Diagnosis

- Gray homogeneous tenacious pseudo-membrane at portal of entry
- Sore throat nasal discharge boariness malaise fever
- Myocarditis neuritis
- Culture confirms diagnosis

Differentiate from streptococcal tonsillitis with its fiery red extremely sore throat and follicular or patchy tonsillar exudate and from other causes of pharyngitis such as infectious mononucleosis adenovirus pharyngitis agranulocytic angina and Vincent's angina. However the presumptive diagnosis of diphtheria must be made on clinical grounds without waiting for laboratory verification since immediate treatment is essential.

### General Considerations

Diphtheria is an acute contagious infection caused by *Corynebacterium diphtheriae* which usually attacks the respiratory tract but may involve any mucous membrane or skin wound. The organism usually gains entry through the respiratory tract and is spread chiefly by respiratory secretions from patients with active disease or healthy carriers. The incubation period is 2-7 days. Myocarditis and late neuritis caused by an exotoxin are also characteristic of the infection.

### Clinical Findings

**A. Symptoms and Signs.** Characteristically there is a homogeneous tenacious gray membrane growing rapidly from the tonsil onto the pillars and pharyngeal walls surrounded by a very narrow zone of erythema and a more extensive zone of edema. The pharyngitis is relatively painless during the earliest stages. Early manifestations are mild sore throat fever and malaise rapidly followed by severe signs of toxemia and prostration. The membrane may grow into the larynx and trachea producing respiratory obstruction. Associated edema of the pharynx may add to the respiratory embarrassment.

If myocarditis develops it will be manifested by a rapid thready pulse indistinct heart sounds cardiac arrhythmia and finally cardiac decompensation with falling BP hepatic congestion and associated nausea and vomiting.

With toxic neuritis the cranial nerves are involved first causing nasal speech regurgitating of food through the nose diplopia and

strabismus. The neuritis may progress to involve the intercostal muscles and those of the extremities. Sensory manifestations are much less prominent than motor weakness.

**B. Laboratory Findings.** The urine usually shows protein due to toxic nephritis. Polymorphonuclear leukocytosis is present. Bacterial culture will confirm the diagnosis. Throat smears are often unreliable. Albuminocytologic dissociation of the CSF is noted in post diphtheritic neuritis.

**C. ECG Findings.** In myocarditis the ECG may show an arrhythmia P-R prolongation heart block and inversion of the T waves.

### Complications

Acute otitis media or bronchial pneumonia may occur.

### Prevention

**A. Children.** Give 3 I M injections (0.5 ml each) of diphtheria toxoid (alum precipitated or aluminum hydroxide-adsorbed) at 2 months 3 months and 4 months of age. Diphtheria immunization may be combined with tetanus and pertussis immunization (DPT). Follow by Schick test at 3-6 months. Give 0.5 I M as recall injection at one year of age then at 3 years after the primary course and at 7 years after the primary course and then every 4 years.

**B. Adults.** Moloney test for sensitivity to toxoid 0.1 ml of 1:20 dilution of plain toxoid intradermally. Read like the Schick test at 24-48 hours. If the Moloney test is negative proceed with immunization as in children. If the Moloney test is positive give 0.1 ml of 1:10 dilution of toxoid intracutaneously at intervals of 3 weeks for 3 doses.

### Treatment

#### A. Specific Measures

1. Diphtheria antitoxin must be given in all cases when diphtheria cannot be excluded by

Diphtheria Antitoxin Dosage Schedule

Location	Child	Adult
Anterior nasal	5000 units	10 000 units
Mild pharyngeal	10 000 units	20 000 units
Moderate pharyngeal	20 000 units	40 000 units
Severe pharyngeal and nasopharyngeal	40 000 units	80 000 units
Laryngeal	10 000 units	20 000 units
Any 2 sites or late cases	40 000 units	80 000 units

simple clinical examination. The I.V. route is preferable in all but the mildest cases or in patients who are sensitive to horse serum. Conjunctival and skin tests for serum sensitivity should be done in all cases, and desensitization carried out if necessary (see p 666). The dose varies with the duration of the disease, the location of the lesion, and the size of the patient. A single dose should suffice.

2 Procaine penicillin, 300,000 units I.M. daily, accelerates slightly the disappearance of the organism from the throat and acts against secondary streptococcal invaders, it does not alter the course of the disease itself.

B General Measures Place the patient at absolute bed rest for at least 3 weeks and until the ECG is normal. Give a liquid to soft diet as tolerated, hot saline or 30% glucose throat irrigations 3-4 times daily, and aspirin or codeine as required for relief of pain.

### C Special Problems

1 Myocarditis - No definitive treatment is known. Oxygen by tent or mask may be needed. Hypertonic glucose solution, 100 ml of 20% solution daily, may be of value. Digitalis and quinidine should be reserved for arrhythmias with rapid ventricular rate.

2 Neuritis - Nasal feeding should be attempted. Corrective splinting and physical therapy may be of value. Tracheostomy and the use of a mechanical respirator may be necessary.

3 Respiratory tract obstruction - Croupy cough, stridor, and dyspnea suggest laryngeal obstruction. Suction of membrane and secretions under direct laryngoscopy may help. Intubation or tracheostomy should be performed before the appearance of cyanosis if the distress increases.

D Treatment of Complications Acute otitis media and bronchial pneumonia are discussed in Chapters 6 and 7, respectively.

E Treatment of Carriers Penicillin has a limited effect on the carrier state.

### Prognosis

The mortality rate varies between 10 and 30%, it is higher in older persons and when treatment has been delayed. Myocarditis which appears early is often fatal. Disturbances of conduction or the appearance of an arrhythmia implies a poor prognosis. Neuritis is rarely fatal unless respiratory muscle paralysis occurs. Myocarditis and neuritis will subside slowly but completely if the patient survives.

Brainerd, H., & H B Bruyn Diphtheria  
The present-day problem Calif Med 75  
290-5, 1951

## PERTUSSIS (Whooping Cough)

### Essentials of Diagnosis

- Paroxysmal cough ending in a high-pitched inspiratory "whoop"
- Two-week prodromal catarrhal stage of malaise, cough, coryza, and anorexia
- Predominantly in infants under 2 years of age
- Absolute lymphocytosis
- Culture confirms diagnosis

The catarrhal stage must be distinguished from bronchitis or influenza. Lymphocytosis occurring in an afebrile child may raise the question of acute leukemia.

### General Considerations

Pertussis is an acute, highly communicable infection of the respiratory tract caused by *Hemophilus pertussis*. It is transmitted by respiratory droplets from infected individuals. The incubation period is 7-14 days. Infectivity is greatest early in the disease and decreases until the organisms disappear from the nasopharynx (after about one month). Infants are most commonly infected, half of all cases occur before 2 years of age.

### Clinical Findings

A Symptoms and Signs Physical findings are minimal or absent. Fever, if present, is low-grade. Although atypical cases lasting only a few days to a week have been described, the symptoms of classical pertussis last about 6 weeks and are divided into 3 consecutive stages.

(1) Catarrhal stage The onset is insidious, with lacrimation, sneezing, coryza, anorexia, malaise, and a hacking night cough which tends to become diurnal.

(2) Paroxysmal stage This follows the beginning of the catarrhal stage by 10-14 days, and is characterized by rapid consecutive coughs usually followed by a deep hurried inspiration (whoop). Paroxysms may involve 5-15 coughs before a breath is taken, and may occur up to 50 times in 24 hours. Psychic stimuli such as fright or anger, crying, sneezing, inhalation of irritants, and overdistention of the stomach may produce the paroxysms.

The cough is productive of copious amounts of thick mucus. Vomiting is common during the paroxysms.

(3) **Convalescent stage** This stage usually begins 4 weeks after the onset of the illness, and is manifested by a decrease in the frequency and severity of paroxysms of cough.

**B Laboratory Findings** The WBC is usually 15,000-20,000/cu mm (rarely, to 50,000), 60-80% lymphocytes. Culture and identification of the causative organism by cough plate or nasopharyngeal swab is possible in 70% of cases.

#### Complications

**Asphyxia** the most common complication, occurs most frequently in infants and may lead to convulsions and brain damage. The increased intracranial pressure during a paroxysm may also lead to brain damage by causing cerebral hemorrhage. Pneumonia, atelectasia, interstitial and subcutaneous emphysema and pneumothorax may occur as a result of damaged respiratory mucosa, inspissated mucus, or increased intrathoracic pressure.

#### Prevention

**A Passive prophylaxis** of exposed susceptibles may usually be accomplished by the injection of 20 ml of hyperimmune serum or 2.5 ml of hyperimmune gamma globulin, I M.

**B Active immunity** may be produced with a vaccine containing 40 billion phase I organisms/ml. Give 3 injections of 0.5 ml each I M at monthly intervals beginning at 2-6 months of age. The vaccine may be combined with diphtheria and tetanus toxoids.

#### Treatment

##### A Specific Measures

1. **Antibiotics** - Give one of the following (1) Tetracycline drugs, 25-50 mg/Kg/day orally (2) Streptomycin, 1 Gm/day I M in divided doses for 1 week (3) Chloramphenicol (Chloromycetin®), 50 mg/Kg/day orally (4) Erythromycin, 30 mg/Kg/day orally.

2. **Hyperimmune serum or hyperimmune gamma globulin** appear to hasten recovery, prevent complications, and reduce mortality. Give 20 ml hyperimmune serum or 2.5 ml hyperimmune gamma globulin daily or every other day I M for 4 or 5 doses.

##### B General Measures

1. **Nutrition** - Frequent small feedings may be necessary. Re-feed if vomiting occurs shortly after a meal. A high-caloric formula by gavage tube may be required in infants who to eat. Parenteral fluids may be used

to ensure adequate fluid intake in severe cases.

2. **Cough** - Sedative and expectorant cough mixtures are of slight benefit. Atropinization to the point of facial flushing with increasing doses of tincture of belladonna every 4 hours, starting with one drop, is occasionally helpful. Ether in oil by rectum may be used in severe cases.

##### C Treatment of Complications

1. **Pneumonia**, usually due to secondary invaders, should be treated with hyperimmune serum or gamma globulin (see above), penicillin and sulfonamides, or streptomycin. Oxygen is often required.

2. **Convulsions** may require sedation, 100% oxygen inhalation, and lumbar puncture.

#### Prognosis

In children under one year of age the mortality rate until recently was over 20%, this rate has been reduced to 1-2% with antibacterial therapy. Bronchiectasis is a fairly common sequel.

Kaufman, S., & H B Bruyn. *Periussis* - a clinical study. *Am J Dis Child* 98:417-22, 1960.

## INFECTIONS OF THE CNS

Infections of the CNS can be caused by almost any infectious agent, but most commonly are due to pyogenic bacteria, mycobacteria, fungi, spirochetes, and viruses. Certain symptoms and signs are more or less common to all types of CNS infection: headache, fever, sensorial disturbances, neck and back stiffness, positive Kernig's and Brudzinski's signs, and CSF abnormalities. In patients presenting with these manifestations the possibility of CNS infection must be considered and, when possible, the specific cause established by means of a careful history and physical examination as well as study of the CSF and other appropriate laboratory procedures.

CNS infections must not be confused with meningismus, which consists of the signs of meningeal irritation in the absence of meningeal inflammation. Meningismus occurs with certain febrile diseases such as streptococcal pharyngitis, pneumonia, and bacterial enteritis in children.

#### Etiologic Classification

CNS infections can be divided into 3 broad categories which usually can be readily distinguished from each other by CSF examina-

tion as the first step toward etiologic diagnosis (see chart below).

A. Purulent Meningitis: E.g., due to infection with meningococci (40% of cases), pneumococci, streptococci, Hemophilus influenzae, staphylococci, and gonococci

B. Granulomatous Meningitis. E.g., due to Mycobacterium tuberculosis, Coccidioides, Cryptococcus, Histoplasma, and other fungi, or Treponema pallidum (meningovascular syphilis).

C. Viral Meningitis: E.g., due to the viruses of the following diseases: poliomyelitis, arthropod-borne encephalitis, "post-infectious" encephalitis, lymphocytic choriomeningitis, mumps, rabies, and infectious mononucleosis, and to Coxsackie or ECHO virus infection

The aseptic meningitis syndrome is of diverse etiology and presents the clinical and CSF findings of viral meningitis in the absence of the specific clinical phenomena diagnostic of a particular disease. e.g., lower motor neuron paralysis in poliomyelitis, salivary gland involvement in mumps, or marked sensorial disturbances in encephalitis. Among the important causes of the aseptic meningitis syndrome are nonparalytic poliomyelitis, mumps, leptospirosis, and Coxsackie and ECHO viral infections

### Laboratory Diagnosis

Clinical descriptions of the various forms of CNS infections will be found elsewhere in the book. Although a history of exposure to disease or vectors, the presence of infections outside the CNS, rashes, neurologic abnormalities, blood culture, skin tests, serologic tests, and other clues are important in differential diagnosis, examination of the CSF is the

single most useful tool in the diagnosis of CNS infections.

Brainerd, H.: Infections of the central nervous system: An approach to diagnosis. J. Pediat. 37:478-83, 1950

Smith, M.H.: Acute bacterial meningitis. Pediatrics 17:258-77, 1956.

## 1. MENINGOCOCCIC MENINGITIS

### Essentials of Diagnosis.

- Fever, headache, vomiting, confusion, delirium, convulsions
- Petechial rash of skin and mucous membranes.
- Neck and back stiffness with positive Kernig's and Brudzinski's signs.
- Purulent spinal fluid with gram-negative intracellular and extracellular organisms
- Culture of CSF, blood, or petechial aspiration confirms the diagnosis

Meningococcic meningitis must be differentiated from other meningitides. In small infants the clinical manifestations of meningeal infection may be erroneously diagnosed as upper respiratory infection or other acute infections

### General Considerations.

Meningococcic meningitis is caused by Neisseria meningitidis and results from a bacteremia originating in a nasopharyngeal focus localizing in the meninges. The infection is spread by respiratory droplets from patients with active disease, i.e., those with mild upper respiratory meningococcic infections and, principally, apparently healthy

Typical CSF Findings in Various CNS Diseases

Type of Infection	Cells/cu mm	Cell Type*	Pressure	Protein (mg./100 ml.)	Glucose (mg./100 ml.)	Chloride (mg./100 ml.)
Purulent meningitis	> 1000	PMN	+++	> 100	< 40	< 720
Granulomatous meningitis	< 1000	L†	+++	> 100	< 40	< 720
Viral infection	< 1000	L†	Normal to +	< 100	> 40	> 720
"Neighborhood" reaction‡	Variable	Variable	Variable	Variable	> 40	> 720

\*PMN = polymorphonuclear neutrophil, L = lymphocyte.

†PMN's may predominate early

‡May occur in mastoiditis, sinusitis, brain abscess, brain tumor, epidural abscess

carriers (a 10-30% carrier incidence has been observed during epidemics). The bacteremia (meningococcemia) may not be clinically evident, or may be fulminating and rapidly fatal with little or no evidence of meningitis. The meningococcemia may also be associated with adrenal hemorrhage (Waterhouse-Friderichsen syndrome). The incubation period is 3-7 days, with infectivity occasionally present for several days before the appearance of the meningitis.

#### Clinical Findings.

**A. Symptoms and Signs** High fever, chills, and headache, back, abdominal, and extremity pains, and nausea and vomiting are present. In severe cases rapidly developing confusion, delirium and coma occur. Convulsive twitchings or frank convulsions may also be present.

Nuchal and back rigidity are present, with positive Kernig's and Brudzinski's signs. A petechial rash is found in most cases. Petechiae may vary from pinhead-sized to large ecchymoses or even areas of skin gangrene which may later slough if the patient survives. These petechiae are found in any part of the skin, mucous membranes, or the conjunctivae, but never in the nail beds, and they usually fade in 3-4 days. The increased intracranial pressure will cause the anterior fontanel to bulge (if not closed) and may produce Cheyne-Stokes or Biot's respiration.

**B Laboratory Findings** Leukocytosis is usually marked. The urine may contain protein, casts, and red cells. Lumbar puncture reveals a cloudy to frankly purulent CSF, with elevated pressure, increased protein, and decreased glucose and chloride content. The fluid usually contains more than 1000 cells/cu mm, with polymorphonuclear cells predominating and containing gram-negative intracellular cocci. The absence of organisms in a gram-stained smear of the CSF sediment does not rule out the diagnosis but in fact favors meningococcal etiology in a purulent meningitis. The organism is usually demonstrated by smear or culture of the CSF, oropharynx, blood, or aspirated petechiae.

#### Complications.

Arthritis, cranial nerve damage (especially the eighth nerve, with resulting deafness), internal hydrocephalus, and iritis may occur as complications.

#### Prevention

Give 1-2 Gm of sulfadiazine orally to exposed persons or carriers in 2 doses taken on the same day.

#### Treatment.

##### A. Specific Measures

1 Sulfonamides are the agents of choice. In severe cases give sodium sulfadiazine, sodium sulfamerazine, or a mixture of equal parts of each, or sulfisoxazole, 5 Gm in 1000 ml of an electrolyte solution, preferably Ringer's lactate solution, I V or subcut by clysis at once. In mild cases give sulfadiazine, sulfamerazine, sulfmethazine, or a mixture of equal parts of each, or sulfisoxazole, 3 Gm orally with adequate fluids to prevent crystal formation. Follow with 3 Gm I V or subcut every 8-12 hours or 1 Gm orally every 4-6 hours as indicated by severity.

2 Penicillin - In addition to sulfonamides give aqueous penicillin, 100,000 units I M every 3 hours, or procaine penicillin G, 600,000 units I M twice daily.

Antibacterial therapy need be continued only one week.

**B General Measures** Give paraldehyde, sodium amobarbital (I V), or morphine sulfate as necessary for restlessness, and restraints, if necessary, for marked restlessness. Fluid intake should be at least 3 L daily and should be sufficient to maintain a urinary output of at least 1000-1500 ml. Replace fluid lost by vomiting and give parenterally if necessary. If the patient is comatose more than 3 days, give feedings (and medication) by stomach tube. Repeat lumbar puncture if evidence of increased intracranial pressure persists or to check the response to therapy by CSF glucose level. Treat shock as outlined on p. 3.

#### Prognosis

The over-all mortality of meningococcal meningitis is 10%. Young healthy individuals and those who retain consciousness usually survive.

Banks, H S Meningococcosis, a protean disease. *Lancet* 2: 635-40 and 677-81, 1948.

## 2. PNEUMOCOCCIC, STREPTOCOCCIC, & STAPHYLOCOCCIC MENINGITIS

The symptoms are similar to those of meningococcal meningitis, but a preceding infection is usually present and a focus is often demonstrable in the lungs (pneumococcal), the middle ear, or sinuses. The CSF must be cultured and examined to determine the causative agent.

Specific treatment of pneumococcal and streptococcal meningitis consists of aqueous penicillin, 1 million units I.M. every 2 hours or by continuous I.V. drip. In severe cases it may also be necessary to give 10,000 units of penicillin in 10 ml. of physiologic saline once daily intrathecally until the CSF glucose is normal. Treat staphylococcal meningitis with combined penicillin, bacitracin, erythromycin, novobiocin, and chloramphenicol pending results of sensitivity tests (see Staphylococcal Pneumonia), or with methicillin (Staphicillin®), 10-12 Gm. daily I.V. or I.M.

With adequate and at times very large doses of antibiotics, the mortality rate is strikingly reduced. Staphylococcal meningitis carries the gravest prognosis.

Haggerty, R.J., & M. Zlat. Antibiotics and bacterial meningitis. *Pediatrics* 25:742-7, 1960.

### 3. TUBERCULOUS MENINGITIS

#### Essentials of Diagnosis.

- Gradual onset of listlessness, irritability, and anorexia
- Headache, vomiting, coma, convulsions, neck and back rigidity
- Tuberculous focus usually evident elsewhere
- Usually in children below 5 years of age
- CSF with web and pellicle showing organisms by smear or culture

*Tuberculous meningitis may be confused with any other meningitis, but the gradual onset and evidence of tuberculosis elsewhere usually help to clarify the diagnosis.*

#### General Considerations.

Tuberculous meningitis is caused by meningeal spread of the tubercle bacilli from a gross or microscopic focus usually in the lungs or the peritracheal, peribronchial, or mesenteric lymph nodes, or as a result of miliary spread. Its greatest incidence is in children between the ages of one and 5 years.

#### Clinical Findings.

A. Symptoms and Signs. The onset is usually gradual, with listlessness, irritability, anorexia, and fever, followed by headache, vomiting, night cries, convulsions, and coma. In older patients headache and behavioral changes are prominent early symptoms.

Nuchal rigidity, opisthotonos, and paralysis occur as the meningitis progresses. Paralysis of the extraocular muscles is common. Ophthalmoscopic examination may reveal choroid tubercles. General physical examination may reveal evidence of tuberculosis elsewhere. The tuberculin skin test may be negative in miliary tuberculosis.

B. Laboratory Findings. The CSF is frequently xanthochromic, with increased pressure and 50-500 cells/cu mm (early, polymorphonuclear neutrophils, later, lymphocytic), decreased glucose, and decreased chloride content. On standing the CSF may form a web and pellicle from which organisms may be demonstrated by smear, culture, or guinea pig inoculation. Moderate leukocytosis is common. Chest x-ray often reveals a tuberculous focus.

#### Complications

After recovery there may be residual brain damage resulting in motor paralysis, convulsive states, mental impairment, and abnormal behavior. The incidence of these complications increases the longer therapy is withheld. Ataxia and deafness are most often due to streptomycin therapy.

#### Treatment.

A. Specific Measures. Give streptomycin, 30 mg /Kg /day I.M. in divided doses every 6-12 hours for 5 months, and 2 mg /Kg intrathecally daily for 2 weeks, every other day for 2 weeks, and twice a week for 2 weeks (Intrathecal therapy probably is unnecessary if isoniazid is used). In addition to streptomycin, give isoniazid, 10 mg /Kg /day in 2-4 doses for one year, and aminosalicylic acid (PAS), 3-5 Gm. every 6 hours by mouth (or sodium para-aminosalicylate, 15-30 Gm. daily I.V.) for one year.

B. General Measures. Treat symptoms as they arise and maintain good nutrition and adequate fluid intake. Treatment with corticosteroids in the early phases needs further evaluation.

#### Prognosis.

The natural course of the disease is death within 6-8 weeks. When it is diagnosed and treated early the recovery rate is up to 90%, if treatment is not instituted until the disease has reached the late stage, the recovery rate is 25-30%.

Treatment of tuberculous meningitis. A comparative trial by a Scottish joint committee, *Lancet* 2:756-60, 1957.

#### 4. HEMOPHILUS INFLUENZAE MENINGITIS

##### Essentials of Diagnosis

- Fever, malaise, headache, vomiting
- Nuchal and back rigidity
- Usually occurs in children under 2 years of age
- Leukocytosis, gram-negative rods in the CSF, type-specific capsule swelling test
- Culture confirms diagnosis

It is impossible to distinguish *Hemophilus influenzae* meningitis from other purulent meningitides on the basis of symptoms and signs but the discovery and identification of the specific organism in the CSF makes exact diagnosis possible

##### General Considerations

This rather common meningitis is due almost entirely to the type B strain of *Hemophilus influenzae*. It occurs most frequently in infants under 2 years of age

##### Clinical Findings

Nothing about the onset, symptoms, or signs distinguishes this illness from other purulent meningitides. It may exist for several days as an apparent respiratory infection, however, irritability, fever, unexplained leukocytosis, and some nuchal rigidity should suggest meningitis. Lumbar puncture will reveal the gram-negative pleomorphic rods in the purulent spinal fluid smear or culture. A capsule-swelling test can be performed on any organisms found if antiserum is available

##### Treatment.

**A. Specific Measures** Give streptomycin (adults, 1 Gm., children 250 mg.) I.M. every 6 hours for one week, and streptomycin, 25 mg. in 10 ml. of physiologic saline solution intrathecally daily until the CSF glucose is normal. In some cases give also sulfadiazine, sulfamerazine, sulfamethazine, or a mixture of equal parts of each, 150 mg./Kg./day, with adequate fluids to prevent crystal formation. Tetracycline drugs, 0.5 Gm. every 6 hours are of value. Chloramphenicol (Chloromycetin<sup>®</sup>) is also effective

**B. General Measures** Treat symptoms as they arise and maintain good nutrition and adequate fluid intake

##### Prognosis.

Prompt treatment is required to prevent death or permanent CNS damage. Before the advent of chemotherapeutic agents the mortality rate was virtually 100%.

Shaw, E. B., & H. B. Bruyn. Streptomycin in therapy of *Hemophilus influenzae* meningitis. *J. Pediatr.* 56:253-8, 1960

#### TYPHOID & PARATYPHOID FEVER

##### Essentials of Diagnosis

- Gradual onset of malaise, headache, sore throat, cough, and finally "pea-soup" diarrhea or constipation.
- Slow (step-ladder) rise of fever to maximum and then slow return to normal
- Rose spots, relative bradycardia, splenomegaly, and abdominal distention and tenderness
- Leukopenia, positive blood, stool, and urine culture
- Elevated or rising specific (Widal) agglutination titers

Typhoid and paratyphoid fever must be distinguished from other prolonged fevers associated with normal or depressed WBC. For example, tuberculosis, primary atypical pneumonia, and psittacosis are differentiated by the infrequency of pneumonic involvement and the presence of rose spots in typhoid and paratyphoid fever, malaria, subacute bacterial endocarditis, brucellosis, and Q fever are distinguished by finding the specific organisms or by demonstrating a positive serologic titer for the specific organism

##### General Considerations

Typhoid fever is caused by the gram-negative rod *Salmonella typhi*, which enters the patient via the gastrointestinal tract where it penetrates the intestinal wall and produces inflammation of the mesenteric lymph nodes and the spleen. As the defense mechanism of the host is overwhelmed, bacteremia occurs, and the infection eventually localizes principally in the lymphoid tissue of the small intestine (particularly within the 2 feet of the ileocecal valve). These Peyer's patches become inflamed and finally may ulcerate. Ulceration and sloughing reach a maximum during the third week of the disease. Occasionally the organism may localize in the lung, gallbladder,



kidney, or CNS with resulting inflammation. Infection is transmitted by eating or drinking contaminated food or liquid. Most infections are transmitted by chronic carriers with a persistent gallbladder or urinary tract focus. The incubation period is 5-14 days.

Paratyphoid fever is an acute generalized infection caused by any strain of *Salmonella*, although usually *S. paratyphi* and *S. schottmüller* are responsible. Transmission is via contaminated food and liquids.

### Clinical Findings

Paratyphoid fever, although it is usually milder and has a shorter incubation period and a more abrupt onset than typhoid fever, is clinically and pathologically indistinguishable from typhoid fever.

**A Symptoms and Signs** In most instances the onset is insidious, less commonly, but especially in children, the onset may be abrupt with chills and a sharp rise in temperature. The course of classical untreated typhoid fever can be divided into 3 stages.

(1) *The prodromal stage* During the period of invasion the patient gradually begins to feel unwell. Increasing malaise, headache, cough, general body aching, sore throat and epistaxis are common. Frequently (but not invariably) there are symptoms referable to the gastrointestinal tract, including abdominal pain, constipation or diarrhea and vomiting. During this period the fever ascends in a step-ladder fashion, the maximum temperature on each day being slightly higher than the preceding day. In the evening the temperature is generally higher than in the morning.

(2) *The fastigium* After about 7-10 days the fever stabilizes, varying less than 2° F during the day, and the patient becomes quite sick. Symptoms referable to the intestinal tract ("pea-soup" diarrhea or severe constipation, or marked abdominal distention) are common. Severe cases enter what is known as the typhoid state, in which the patient lies motionless and unresponsive, with eyes half-shut, appearing wasted and exhausted. He can usually be aroused to carry out simple commands.

(3) *The stage of defervescence* If the patient survives the severe toxemia of the second stage of the disease, or does not die of complications, his condition gradually improves. The fever declines in a "mirror image" of the onset, usually requiring 7-10 days to reach normal. The patient gradually becomes more alert and his abdominal symptoms disappear. During this stage recrudescence or relapse

may occur as late as 1-2 weeks after the temperature has returned to normal. This relapse is usually milder than the original infection, however, occasionally all of the phenomena seen during the fastigium will be duplicated.

During the early prodromal period physical findings are slight or absent. Later, splenomegaly, abdominal distention and tenderness, relative bradycardia, dicrotic pulse, and occasionally meningismus, systolic murmur and gallop rhythm appear. The rash (rose spots) commonly appears during the second week of the disease and may continue to erupt in crops until the period of convalescence. The individual spot is a pink papule 2-3 mm in diameter which fades on pressure. The papules are found principally on the trunk, and there are rarely more than 12. Each spot fades over a period of 3-4 days.

**B Laboratory Findings** Blood cultures may be positive as early as the first week and remain positive for a variable period thereafter (usually as long as the rose spots are present). Stools are positive for the organism after the first week of the disease, the urine may be positive at any time after the first week although the organism is less frequently found in the urine than in the stool.

During the second week of the disease antibodies begin to appear in the blood and continue to rise in titer until about the end of the third week (Widal test). If an anamnestic response to other infectious diseases or recent vaccination is ruled out an O (somatic) antibody titer of 1 to 60 is presumptively diagnostic; a rising titer (as demonstrated by 2 specimens taken approximately a week apart) is almost completely diagnostic.

Moderate anemia is almost always seen during the height of infection. Leukopenia is the rule. Proteinuria is common.

### Complications

Complications occur in about 30% of untreated cases and account for three-fourths of all deaths. Intestinal hemorrhage is most likely to occur during the third week and is manifest by a sudden drop in temperature, rise in pulse, and signs of shock followed by dark or fresh blood in the stool. Intestinal perforation is most likely to occur during the third week. Sudden rigor, drop in temperature, and increase in pulse rate, accompanied by abdominal pain and tenderness, may be noted. Less frequent complications include urinary retention, pneumonia, thrombophlebitis, myocarditis, psychosis, cholecystitis, nephritis, spondylitis (typhoid spine), and meningitis.

**Prevention**

A Typhoid vaccine (1 billion organisms/ml) 0.5 ml, 1 ml, and 1 ml subcut at weekly intervals, is usually given with paratyphoid A and B vaccine. Intradermal injection of 0.1 ml at weekly intervals may be used to minimize unfavorable reactions.

B Drinking water and milk must be boiled during an epidemic.

C Carriers must be rigidly controlled and not permitted to be food handlers.

**Treatment**

A Specific Measures Give chloramphenicol (Chloromycetin®) 1 Gm orally every 4 hours until fever disappears and then 0.5 Gm every 6 hours (In children give 50 mg/Kg/day followed by 25 mg/Kg/day when afebrile). Continue treatment for 3 weeks. Hydrocortisone 20 mg orally every 6 hours, may be used temporarily in severely toxic patients.

B General Measures Prevent decubiti by careful bathing, skin massage, and use of rubber "doughnuts" over pressure areas. Careful oral hygiene is important.

Give a high-calorie, low-residue diet (approximately 3800-4800 Calories/day). Complete vitamin supplementation must be used. The Coleman diet (about 1500 Calories/L) consists of lactose 400 Gm, cream 800 ml, and milk, 2800 ml. The casein hydrolysate formula (about 1050 Calories/L) consists of casein hydrolysate 125 Gm, and milk 1 L.

Parenteral glucose solution may be necessary to supplement fluid intake and maintain urine output. Abdominal distention may be relieved by gentle colonic flushes and abdominal atropes. Vasopressin and neostigmine must be used with great caution because of the danger of perforation.

Diarrhea may be controlled with bismuth subcarbonate or camphorated tincture of opium.

The patient must be strictly isolated and his excreta sterilized until negative stool cultures have been obtained.

C Treatment of Complications Secondary pneumonia may be treated with penicillin, sulfonamides, streptomycin, or tetracycline drugs, depending on the etiologic agent.

Transfusions should be given as required for hemorrhage. If perforation occurs, immediate surgery is required. Anticipate and treat shock (see p. 3) before it is manifest.

D Treatment of Carriers Chemotherapy is usually ineffective in abolishing the carrier state.

**Prognosis**

The mortality rate of typhoid fever is about 2% in treated cases. Elderly or debilitated persons are likely to do poorly. In children the course is milder.

With complications the prognosis is poor. Relapses occur in up to 15% of cases. A residual carrier state frequently persists in spite of chemotherapy.

Eisenberg, G. M., & others. Clinical and microbiological aspects of salmonellosis. *Am J M Sc* 235:497-509, 1958.

Woodward, T. E., Smadel, J. E., & R. T. Parker. Therapy of typhoid fever. *M Clin North America* 36:577-90, 1954.

**BRUCELOSIS****Essentials of Diagnosis**

- Vague complaints of easy fatigability, headache, arthralgia, anorexia, sweating, and irritability, all of insidious onset.
- Intermittent fever especially noted at night may become chronic and undulant.
- Cervical-axillary lymphadenopathy, splenomegaly.
- Lymphocytosis, positive blood culture, elevated agglutination and complement fixation titer.

Brucellosis with an acute onset must be differentiated from influenza and other acute febrile diseases. In its more common insidious onset it must be distinguished from tularemia, Q fever, and typhoid fever. In its chronic form differentiation from Hodgkin's disease, tuberculosis, and malaria may be necessary. Also in the chronic form it must be differentiated from psychoneurosis either present without prior brucella infection or psychoneurosis remaining as a residual after entire recovery from the infection itself.

**General Considerations**

The infection is caused by any of 3 species of *Brucella* organisms: *Brucella abortus* (cattle), *Brucella suis* (hogs), and *Brucella melitensis* (goats). Transmission to man is by direct contact with excretions and secretions of infected animals. The organism gains entry into man through minor skin abrasions or ingestion of raw contaminated milk or milk products.

Human-to-human transmission is rare. The disease is mainly occupational among meat handlers, farmers, and veterinarians. Children are more resistant to infection than are adults. The incubation period varies from 5 to 20 days, although the time between exposure and overt disease may extend up to several months. The disorder may become chronic and persist for years.

### Clinical Findings

**A Symptoms and Signs** The onset may be acute, with fever, chills, and sweats similar to those seen in any acute febrile illness but in most instances the disease begins so insidiously that it may be weeks before the patient presents himself to the physician with vague symptoms - often of weakness and exhaustion upon minimal activity. Symptoms also include headache, abdominal pains with anorexia and constipation, and arthralgia sometimes associated with periarticular swelling but not local heat. The fever may be septic, sustained, undulating, low-grade, or even absent, but is more often of the intermittent type preceded by a feeling of chilliness, rising during the evening hours and falling with a sweat (night sweat) in the early morning hours. In the chronic form it may assume an undulant nature, with periods of relatively absent fever between acute attacks. In the chronic form the above symptoms plus emotional instability and irritability and weight loss may persist for years either on a continuous or intermittent basis.

Physical findings are minimal. Half of cases have peripheral lymph node enlargement and splenomegaly; hepatomegaly is less common.

**B Laboratory Findings** The WBC is usually normal to low, with a relative or absolute lymphocytosis. The organism can be recovered from the blood, CSF, urine, and tissue, however, this may be difficult, and an agglutination titer greater than 1:100 (and especially a rising titer) is usually used as laboratory verification of the disease. The intradermal skin test is of no value in diagnosing active disease and may confuse the agglutination titers.

### Complications

The most frequent complications are bone and joint lesions such as spondylitis and suppurative arthritis, usually of a single joint, subacute bacterial endocarditis, encephalitis, and meningitis. Less common complications are pneumonitis with pleural effusion, hepatitis, and cholecystitis. Abortion in humans

is no more common with this disease than with any other acute bacterial disease during pregnancy.

### Prevention

Preventive measures consist of destruction of infected dairy animals and immunization of susceptible animals, and pasteurization of all milk and milk products.

### Treatment

**A Specific Treatment** The effectiveness of tetracycline drugs, chloramphenicol, and streptomycin-sulfonamide therapy has not been entirely established in chronic brucellosis. (1) A combination of streptomycin 2 Gm I M daily and one of the tetracycline drugs, 2 Gm orally daily is probably the treatment of choice. (2) Tetracycline drugs 50 mg orally once the first day, 50 mg twice the second day, 50 mg 3 times the third day, and 0.5-1 Gm every 6 hours for the following 12-14 days. (Small initial dosage avoids Herxheimer-like reaction.) (3) Chloramphenicol (Chloromycetin<sup>®</sup>) 50 mg/Kg orally initially and then 0.25 Gm every 3 hours until the patient has been afebrile for 7 days. (4) Streptomycin, 0.5 Gm I M every 6 hours for 2 weeks and sulfadiazine-sulfamerazine-sulfamethazine mixture 3 Gm initially and 1 Gm every 6 hours for 2-3 weeks.

**B General Measures** Place the patient at bed rest during the acute febrile stage and maintain a high vitamin intake.

### Prognosis

In a few cases brucellosis may remain active for many years as an intermittent illness, but about 75% recover completely within 3-6 months and fewer than 20% have residual disease after one year. Treatment has considerably shortened the natural course of the disease.

Brucellosis is rarely fatal either in the acute or the chronic form. Residual psychoneurosis is common in recovered patients.

Spink, W W. The Nature of Brucellosis.  
Univ. of Minnesota, 1956.

## GAS GANGRENE

### Essentials of Diagnosis

- Sudden onset of pain and edema in area of wound contamination
- Brown to blood-tinged watery exudate, with skin discoloration of surrounding area
- Gas demonstrated in the tissue by palpation or x-ray
- Organisms demonstrated on culture or smear of exudate

Other types of infection can cause gas formation in the tissue, e.g. *Aerobacter* and *Escherichia* infections. These organisms produce much more gas than *Clostridia*.

### General Considerations

Gas gangrene is an infection caused by any of several anaerobic gram-positive bacilli which gain entry into the tissue by dirt or fecal contamination of wounds, usually those containing devitalized tissue. The puerperal tract may be infected. The organism grows only in anaerobic conditions, producing a toxin which spreads into and destroys the surrounding tissues and thus creates increasing areas of reduced oxygen tension into which the organisms may advance. In the process gas is produced. It is probable that the entire infection is a local reaction, although the possibility of toxins invading the blood and affecting distant vital centers has been postulated. The incubation period is 6 hours to 3 days after injury.

### Clinical Findings

**A Symptoms and Signs** The onset is usually sudden, with rapidly increasing pain in the affected area accompanied by a fall in BP, and tachycardia. The temperature may be elevated, but not proportionate to the severity of the inflammation. In the last stages of the disease severe prostration, stupor, delirium, and coma occur.

The wound becomes swollen, and the surrounding skin is pale as a result of fluid accumulation beneath it. This is followed by a discharge of a brown to blood-tinged, serous foul-smelling fluid from the wound. As the disease advances the surrounding tissue changes from pale to dusky to finally become deeply discolored with coalescent red, fluid-filled vesicles. Gas may be palpable in the tissues. In clostridial septicemia, hemolysis and jaundice are common.

**B Laboratory Findings** Gas gangrene is a clinical rather than a bacteriologic diagnosis although culture of the exudate confirms the diagnosis and stained smear of the exudate showing the typical gram-positive rods is a valuable clue to the diagnosis.

**C X-ray** may show gas in the soft tissues spreading along fascial planes.

### Treatment

**A Specific Measures** Give penicillin 100,000 units I.M. every 3 hours, polyvalent gas-gangrene antitoxin, 20,000 units stat and repeat every 6-8 hours, and full doses of sulfadiazine-sulfamerazine-sulfamethazine mixture (see p. 655).

**B Surgical Measures** Adequate surgical debridement and exposure of infected areas.

### Prognosis

Without treatment the disease is invariably fatal.

Altmeier, W. A., & others. Problems in the diagnosis and treatment of gas gangrene. *Arch Surg* 74:839-45, 1957.

## ANTHRAX

Anthrax is a disease of sheep, cattle, horses, goats and mules caused by *Bacillus anthracis*, a gram-positive sporeforming bacillus which is transmissible to man by entry through broken skin or mucous membranes or, less commonly, by inhalation. Human infection is rare. It is most common in farmers, veterinarians and tannery and wool workers. Several clinical forms have been observed.

### Clinical Findings

#### A Symptoms and Signs

1. Cutaneous anthrax ("malignant pustule") - An erythematous patch appears on an exposed area of skin, and becomes papular and then vesicular, with a firm, purple to black center. The area around the lesion is swollen or edematous, consisting of a dense ring surrounded by vesicles. The center of the lesion finally forms a necrotic eschar and sloughs. Regional adenopathy, variable fever, malaise, headache, and variable nausea and vomiting are present. Septicemic spread may occur after the eschar sloughs, at times manifested by shock, cyanosis, sweating, and collapse. Cerebral hemorrhage may occur.

2 Malignant edema - This form of the disease is characterized by fever, malaise, and rapidly spreading edema of the skin or mucous membranes followed by sloughing and gangrene

3 Pulmonary anthrax ("wool sorter's disease") - Characterized by fever, malaise, headache, dyspnea, cough, congestion of the nose, throat, and larynx, and auscultatory or x-ray signs of pneumonia

**B Laboratory Findings** The WBC may be elevated or low. Sputum or blood culture may be positive for *Bacillus anthracis*. Smears of skin lesions show gram-positive rods.

#### Treatment.

Give procaine penicillin G 1-2 million units I.M. daily, or one of the tetracyclines, 0.5 Gm orally every 6 hours.

#### Prognosis

The prognosis is excellent in the cutaneous form of the disease if treatment is given early. Malignant edema and pulmonary anthrax have a grave prognosis. Bacteremia is a very unfavorable sign.

Gold, H. Anthrax. A report of one hundred seventeen cases. Arch Int Med 95:387-98, 1955.

## TETANUS

#### Essentials of Diagnosis

- Jaw stiffness followed by spasms of jaw muscles (trismus)
- Stiffness of the neck and other muscles; dysphagia, irritability, hyperreflexia
- Finally, painful convulsions precipitated by minimal stimuli
- History of wound and possible contamination

Differentiate from acute CNS infections such as poliomyelitis and rabies, in which trismus is absent, and from infections of the throat and jaw in which trismus may be present due to local causes. Strychnine poisoning and tetany due to other causes must also be considered in the differential diagnosis.

#### General Considerations.

Tetanus is an acute CNS intoxication caused by fixation in the CNS of a toxin elab-

orated by the slender, sporeforming, gram-positive, anaerobic bacillus, *Clostridium tetani*. The organism is found mainly in the soil and in the feces of animals and humans, and enters the body by wound contamination. Although puncture wounds or purulent necrotic lesions are usually contaminated, because the organism is universal in distribution even the most trivial and relatively clean wound may be inoculated.

The exotoxin acts on the motor nerve end plates and anterior horn cells of the spinal cord and brain stem. Once the exotoxin is fixed in the tissue it is doubtful if it can be neutralized. The question of whether the toxin enters the CNS via the blood stream or through motor nerves is still unsettled. The incubation period is 5 days to 15 weeks.

#### Clinical Findings

**A Symptoms and Signs** Occasionally the first symptom is pain and tingling at the site of inoculation followed by spasticity of the group of muscles nearby. This may constitute the entire disease, especially in those individuals treated with inadequate prophylactic doses of antitoxin. More frequently, however, the presenting symptoms are stiffness of the jaw, neck stiffness, dysphagia, and irritability. Hyperreflexia develops later, with spasms of the jaw muscles (trismus) or facial muscles, and rigidity and spasm of the muscles of the abdomen, neck, and back. Painful tonic convulsions precipitated by minor stimuli are common. Although the patient is awake and alert during the entire course of the illness, during convulsions the glottis and respiratory muscles go into spasm so that the patient is unable to breathe and cyanosis and asphyxia may ensue. The temperature is only slightly elevated.

**B Laboratory Findings** The diagnosis of tetanus is made clinically. There is usually a polymorphonuclear leukocytosis.

#### Complications

Malnutrition may occur as a result of dysphagia. Urinary retention and constipation may result from spasm of the sphincters.

#### Prevention

**A Tetanus toxoid**, 1 ml in 3 doses at intervals of 3-4 weeks, followed by a booster of 1 ml at one year and 1 ml at time of injury.

**B Tetanus antitoxin**, 6000 units I.M., in nonimmunized individuals with soil-contaminated wounds, especially puncture wounds, compound fractures, and powder burns. Do not give inadequate doses.

## C Adequate debridement of wounds

D Benzathine penicillin 1 2 million units  
I M

## Treatment.

A Specific Measures Tetanus antitoxin  
100,000 units I V Test for sensitivity to  
horse serum

B Place the patient at bed rest and minimize stimulation Sedation and anticonvulsant therapy are essential Experience from India and other areas of high incidence appears to indicate that most convulsions can be eliminated by treatment with chlorpromazine (50-100 mg q i d ) combined with a sedative (amobarbital phenobarbital or meprobamate) Mild cases of tetanus can be controlled with only one or the other Only rarely is general curarization required Other anticonvulsant regimens which have been recommended are as follows (1) Tribromoethanol 15-25 mg / Kg rectally every 1-4 hours p r n (2) Amobarbital sodium 5 mg /Kg I M p r n (3) Paraldehyde 4-8 ml (1-2 dr ) I V (2-5% solution) may be combined with barbiturates Penicillin is of value but should not be substituted for antitoxin

Give I V fluids as required

## Prognosis

The mortality rate is higher in very young and very old people, with shorter incubation periods with shorter intervals between onset of symptoms and the first convulsion and with delay in treatment If trismus develops early the prognosis is grave The over-all mortality is about 40% Contaminated lesions about the head and face are more dangerous than wounds on other parts of the body

If the patient lives, recovery is complete

Garcia-Palmieri, M R , & R Ramirez Generalized tetanus An analysis of 202 cases  
Ann Int Med 47 721-30, 1957

## BOTULISM

## Essentials of Diagnosis

- Sudden onset of cranial nerve paralysis heralded by ocular involvement (especially diplopia)
- History of ingestion of home-canned food or finding the toxin in suspected food
- Blood urine, and CSF findings are normal

Botulism must be differentiated from acute viral CNS infections, especially bulbar poliomyelitis, and from myasthenia gravis, postdiphtheritic neuritis, and infectious neuritis

## General Considerations

Botulism is a food poisoning caused by ingestion of preformed toxin of *Clostridium botulinum* It is characterized by involvement of the CNS, especially of the bulbar region The toxin interferes with the release of acetylcholine by the nerve tissue In the United States most cases follow ingestion of improperly prepared home-canned foods especially vegetables and meats The toxin is heat-labile and is destroyed by proper cooking of foods

## Clinical Findings

A Symptoms and Signs Symptoms appear abruptly 18-36 hours after the ingestion of the toxin and are usually ushered in by visual disturbances (diplopia, loss of powers of accommodation and reduced visual acuity) This is followed by involvement of the bulbar cranial nerves causing dysphagia, dysphonia and nasal regurgitation The muscles of the extremities become weak, and vertigo is common Sensory involvement is absent, and the sensorium remains clear The temperature is normal unless intercurrent infection occurs

B Laboratory Findings The blood, urine and CSF findings are normal The suspected food may be examined for the causative toxin by injection into mice

## Complications

Difficulty in swallowing often causes aspiration pneumonia Respiratory paralysis may lead to death

## Prevention

All canned foods must be sterilized Home-canned foods must be boiled for 5-10 minutes before they are eaten Cans with bulging lids or jars with leaking rings should be destroyed

## Treatment.

A Specific Measures Botulinus antitoxin bivalent (Types A and B) 10 000-50,000 units I M as soon as possible

## B General Measures

- 1 Absolute rest with foot of bed elevated to promote drainage from respiratory tract
- 2 Aspiration of respiratory tract frequently Tracheostomy may be required
- 3 Oxygen by mask or catheter as indicated

4. Respirator as required for respiratory paralysis
5. Intravenous fluids as necessary.
6. Treat complicating pneumonia with antibiotics if present

#### Prognosis.

The mortality rate of botulism is 60%. Death occurs in 20 hours to 10 days. There are usually no sequelae, although residual motor weakness may persist for months.

Meyer, K. F. • Newer knowledge on botulism and mussel poisoning. *Am. J. Pub. Health* 21:762-70, 1931.

## TULAREMIA

#### Essentials of Diagnosis

- Sudden onset of fever, chills, nausea, vomiting, and prostration
- Papule progressing to pustule to clean ulcer at the site of inoculation
- Regional lymph node enlargement and suppuration
- History of contact with contaminated wild animals, especially rabbits
- Diagnosis confirmed by culture of ulcer, lymph node drainage, or blood

Tularemia, because of its variety of forms and long duration, must be differentiated in the early stages from any other acute infection, in its pneumonic form from atypical pneumonia and psittacosis, and in its typhoid form from typhoid fever. Because of the long duration of fever, tularemia must also be distinguished from brucellosis. The lymphadenitis must be differentiated from plague, lymphogranuloma venereum, infectious mononucleosis, tuberculosis, and cat-scratch fever. Pathologically the lesions of tularemia must be differentiated from those of tuberculosis.

#### General Considerations.

Tularemia is caused by the gram-negative organism *Pasteurella tularensis*. The infection is acquired by man from infected animals by ingestion of the contaminated meat, contamination of the skin (even unbroken skin), or by bites of insects which have bitten the infected animal. Ninety per cent of cases are traceable to an infected wild rabbit. The lesions consist of areas of focal necrosis scat-

tered throughout the body. The incubation period is 1-10 days (average 2-4 days).

#### Clinical Findings.

**A. Symptoms and Signs** There is a sudden onset of fever, chills, headache, nausea, vomiting, sweats, and severe weakness, followed within 1-2 days by the formation of a papule or papules at the site of inoculation (ulceroglandular form). The papule soon becomes a pustule and finally ulcerates to produce a clean crater. The regional lymph nodes become enlarged, and may ulcerate and drain profusely. An atypical pneumonia with pleurisy (pneumopleuritic form) or a typhoid-like state (typhoidal form), or a combination of both types of involvement, frequently develops within 4-5 days. A nonspecific roseola-like rash may appear at any time. The spleen is frequently enlarged, and a perisplenitis may develop. If the site of inoculation is the eye, conjunctivitis and preauricular adenitis result.

**B. Laboratory Findings** A relative or absolute polymorphonuclear leukocytosis is present. After the third day the intradermal skin test is positive, and after the tenth day the agglutination test is positive. The organism may be recovered and cultured from the blood, lymph node drainage, or ulcer.

#### Complications.

Lung abscess and meningitis due to the tularemia organism has been reported on rare occasions. Pneumonia, meningitis, and peritonitis account for most tularemic deaths.

#### Treatment.

Treatment, in addition to giving symptomatic and supportive measures as required, consists of giving one of the following: (1) tetracycline drugs, 0.5 Gm. every 6 hours orally for 5-10 days, (2) streptomycin, 2 Gm. I.M. daily in divided doses every 6 hours for 5-10 days, or (3) chloramphenicol (Chloromycetin®), 0.5 Gm. orally every 6 hours for 5-10 days.

#### Prognosis.

The over-all mortality rate is 6%, but the mortality rate of untreated pulmonary tularemia is 63%. Death may occur within 4 days to 9 months after the onset. In untreated cases the duration of fever is 3-4 weeks, adenopathy 3-4 months, and the disease itself 5-6 months. Chemotherapy has improved the outlook markedly.

Van Metre, T. E., Jr., & P. J. Kadull: Laboratory-acquired tularemia in vaccinated

individuals a report of 62 cases Ann Int Med 50 621-32, 1959

## PLAGUE

### Essentials of Diagnosis

- Sudden onset of chills fever malaise muscular pains and prostration
- Regional lymphangitis and adenitis with finally suppuration of the nodes
- Septicemia and pneumonitis may occur
- History of contact with infected animals pneumonic human cases
- Confirmation by culture or animal inoculation

The adenitis of plague must be distinguished from the adenitis of streptococcal and staphylococcal infection infectious mononucleosis, syphilis lymphogranuloma venereum tularemia, and cat scratch fever, the septicemic form may be confused with other types of sepsis tularemia typhus typhoid fever and malaria The pneumonic form must be distinguished from viral pneumonitis psittacosis and bacterial bronchial pneumonia

### General Considerations

Plague is an acute epidemic infection caused by the gram-negative bacillus *Pasteurella pestis* which is usually transmitted to man by rodent fleas when the fleas leave the dying animal vector and seek human hosts Transmission is by deposition of contaminated feces on excoriated skin or regurgitation of contaminated blood at the time of feeding The pneumonic form of the disease, however, may be transmitted from man to man by inhalation of infected respiratory tract droplets Sporadic cases occur from contact with infected wild rodents The infection spreads via the lymphatics to the regional lymph nodes and may finally become generalized (septicemic) to involve the brain liver, lungs, and spleen with focal areas of suppuration and necrosis The incubation period is 2-10 days

### Clinical Findings

**A Symptoms and Signs** The onset is usually acute, with high, intermittent fever chills, headache vomiting, generalized muscular pains and mental abnormalities ranging from mental dullness to acute mania The patient exhibits marked anxiety and fear In the pneumonic form there is also tachypnea pro-

ductive cough, and finally cyanosis and blood tinged sputum Epistaxis and gastrointestinal bleeding may occur

A pustule at the site of inoculation is uncommonly found but the signs of a spreading lymphangitis are usually evident Red, tender, and finally suppurative lymph node involvement (buboes) appear on about the second day In the severe form of the disease with septicemia, the characteristic purpuric spots (black plague) appear on the third day The spleen is often palpable

**B Laboratory Findings** The organism may be identified on a methylene blue or Gram stain of material obtained from the buboes the bloody sputum and, more rarely, the blood smear Bacteriologic confirmation is obtained by culture or animal inoculation The x-ray in the pneumonic form shows pulmonary infiltrations The leukocyte count is usually materially elevated

### Complications

Pneumonic plague may occur as a complication of bubonic plague or may exist as a primary form in the case of droplet infections from human contacts Most complications are secondary to bacterial invasion of the draining buboes or of the lung

### Prevention

Prophylactic measures consist of giving plague vaccine (2 billion organisms/ml) 0.5 and 1 ml at intervals of 7-10 days The patient's discharges must be carefully disinfected

### Treatment

Treat as early as possible with streptomycin, 2-6 Gm daily I.M. in divided doses tetracycline drugs 0.5 Gm every 6 hours and sulfadiazine in full doses Give symptomatic and supportive measures as needed

### Prognosis

The disease usually runs its course in 3-6 days The prognosis is extremely variable due to the marked range of severity of the illness, however the mortality rate in untreated cases probably ranges from 25 to 75% The septicemic and pneumonic forms are almost invariably fatal if untreated Chemotherapy has markedly improved the outlook for survival

Meyer, K.F. The natural history of plague and psittacosis Pub Health Rep 72 705 14, 1957



## CHOLERA

### Essentials of Diagnosis.

- Sudden onset of severe, voluminous, frequent diarrhea.
- Vomiting without antecedent nausea
- Diarrhea and vomitus are gray, turbid, and watery (rice water), with little or no blood or pus
- Marked dehydration and electrolyte imbalance, uremia and shock often present
- History of being in an endemic area or contact with an infected individual
- Positive cultures and agglutination reactions

Cholera must be distinguished from other causes of diarrhea, dehydration, and shock, such as bacillary and amebic dysentery, food poisoning, staphylococcal enterocolitis, and infantile diarrhea. Mild cases of cholera are probably misdiagnosed as simple diarrhea or food poisoning.

### General Considerations.

Cholera is an acute dysenteric disease caused by *Vibrio cholerae*. The infection is spread by the ingestion of food or drink contaminated by feces from acute or early convalescent cases. Since warm weather is necessary for survival of the organism in the feces, the infection is usually found in warm countries. The bacillus primarily localizes in the ileum, and the disease is due to a powerful endotoxin liberated on disintegration of the organism. The incubation period is 1-5 days.

### Clinical Findings

**A. Symptoms and Signs** Although mild cases may occur, the typical case begins with a sudden onset of voluminous, frequent, watery stools that soon lose all fecal appearance and become grayish and turbid (rice water), with degenerated epithelium and mucus but with little or no blood or pus. Vomiting without antecedent nausea becomes severe, and soon the individual is unable to retain food or drink and becomes markedly dehydrated, with dry skin, cyanosis, extreme thirst, sunken eyes, and subnormal temperature. Severe muscle cramps may occur, and abdominal cramps are the rule. The urine volume diminishes, and uremia occurs in severe cases.

**B. Laboratory Findings** Routine blood studies show marked dehydration. Very high hemoglobin values (up to 20 Gm/100 ml), and

a WBC up to 25,000/cu mm may be found. The  $\text{CO}_2$  combining power reveals acidosis, and the nonprotein nitrogen may be elevated. The diagnosis is confirmed by isolation of the organism from the stool and identification by agglutination reactions.

### Complications

Secondary infections, especially of the parotid gland, may occur.

### Prevention.

A Cholera vaccine, 0.5 ml initially and then 1 ml subcut after an interval of 7-10 days is indicated for all persons entering endemic areas. Repeat 1 ml every 4-6 months.

**B** Rigid isolation of all cases and careful decontamination of excreta are important. In endemic areas all water and milk must be boiled, and protective screening against flies must be used.

### Treatment.

**A Specific Measures** Give either streptomycin, 1 Gm I.M. every 6 hours, or sodium sulfadiazine or sodium sulfamerazine, 5 Gm in physiologic saline solution I.V. followed by 3 Gm I.V. every 8-10 hours. Oral sulfonamides may be substituted when vomiting ceases. Sodium bicarbonate in equal or double doses should be given with the sulfadiazine or sulfamerazine when the patient is able to swallow.

**B General Measures** Give human plasma and physiologic saline or Ringer's injection, I.V., until shock, dehydration, and anuria are alleviated. Large amounts may be required. Sixth-molar sodium lactate solution may be necessary in severe cases to combat acidosis and to prevent sulfonamide crystal formation in the kidneys. Solutions containing potassium should be given to relieve hypokalemia after initial shock and dehydration are relieved.

### Prognosis.

The untreated disease lasts 3-5 days. The prognosis depends largely upon the previous health of the patient and the adequacy of treatment. The mortality rate in untreated cases averages about 50% (range, 15% to 90%), with prompt treatment the rate may be reduced to 5%.

**Pollitzer, R.** Cholera studies. Symptomatology, diagnosis, prognosis, and treatment. Bull. World Health Organ, 16: 295-430, 1957.

## LEPROSY

### Essentials of Diagnosis

- Pale, anesthetic macular, or nodular and erythematous skin lesions
- Superficial nerve thickening with associated sensory changes
- History of residence in endemic area
- Acid fast bacilli in skin lesions or nasal scrapings or characteristic histologic nerve changes

The skin lesions of leprosy need to be distinguished often from those of lupus erythematosus sarcoidosis syphilis erythema nodosum erythema multiforme and vitiligo nerve involvement, sensory dissociation and resulting deformity may require differentiation from syringomyelia and scleroderma

### General Considerations

Leprosy is a mildly contagious chronic infectious disease caused by the acid-fast rod *Mycobacterium leprae*. The mode of transmission is unknown and attempts to infect human volunteers have been unsuccessful. Susceptibility to leprosy may involve a hereditary factor.

### Clinical Findings

The onset of leprosy is insidious. The lesions involve the cooler tissues of the body: skin, superficial nerves, nose, pharynx, larynx, eyes, and testicles. The skin lesions may occur as pale, anesthetic macular lesions 1-10 cm in diameter, diffuse or discrete erythematous, infiltrated nodules 1-5 cm in diameter, or a diffuse skin infiltration. Neurologic disturbances are manifest by nerve infiltration and thickening, with resultant anesthesia, neuritis, paresthesia, trophic ulcers, and bone reabsorption and shortening of digits. The disfigurement due to the skin infiltration and nerve involvement in untreated cases may be extreme.

The disease is divided clinically and by laboratory tests into 2 distinct types: lepromatous and tuberculoid. In the lepromatous type the course is progressive and malign with nodular skin lesions, slow, symmetric nerve involvement, abundant acid-fast bacilli in the skin lesions, and a negative lepromin skin test. In the tuberculoid type the course is benign and nonprogressive, with macular skin lesions, severe asymmetric nerve involvement of sudden onset with no bacilli present in the lesions, and a positive lepromin

skin test. In the lepromatous type an acute febrile episode with evanescent skin lesions may occur and last for weeks. Eye involvement (keratitis and iridocyclitis), nasal ulcers and epistaxis may occur in both types but are most common in the lepromatous type.

Systemic manifestations of anemia and lymphadenopathy may also occur.

Histologic nerve changes are usually characteristic.

### Complications

Intercurrent tuberculosis is common in the lepromatous type. Amyloidosis may occur with long-standing disease.

### Treatment

Drug therapy must not be given during exacerbations of lesions with much bacillary multiplication and, usually, leprotic fever. Drugs should be given cautiously, with slowly increasing doses, and must be withheld when they show signs of producing an induced exacerbation with leprotic fever, progressive anemia with or without leukopenia, severe gastrointestinal symptoms, allergic dermatitis, hepatitis, or mental disturbances, or erythema nodosum. It is important, therefore, to observe temperature, blood counts and biopsy changes in lesions at regular intervals. The duration of treatment must be guided by progress, preferably as judged by biopsy. Treatment must be continued for several years but often indefinitely because recrudescence may occur after cessation of therapy.

A Diaminodiphenylsulfone (Avlosulfon<sup>®</sup>, DDS) is given orally to a maximum of 600 mg a week for adults in divided doses. If intolerance is feared (commonest in Caucasians or Mongolians with well-developed lepromatous or infiltrated intermediate forms of the disease) start with 50 mg twice weekly and increase to the maximum by 50 mg increments every 2 weeks, by which time the dose of 600 mg weekly may be spread in daily or other fractions. Many selected cases may be treated as out-patients. Children tolerate all the sulfones well in doses proportionate to age (e.g. 300 mg/week for a child of 12). If reaction occurs, stop treatment until recovery is complete and then start again at the beginning or change to another sulfone. (Although all sulfones apparently act in the body in the same way as DDS, some produce fewer reactions.)

B. Sulphathione is best given as 50% aqueous solution, deeply subcut or I.M., in doses be-

gunning with 0.1 ml. twice a week and doubling each 2 weeks to a maximum of 3-5 ml./week in divided doses. An oral preparation is also available; the maximum is 3 Gm. daily.

C. Diphenylthiourea (DPT) is given orally, beginning with 500 mg./day and increasing to a maximum of 2 Gm./day. This drug is indicated if intolerance develops to the above drugs. It may be continued for about 3 years before resistance develops.

#### Prognosis.

Untreated lepromatous leprosy is progressive and fatal in 10-20 years. In the tuberculoid type spontaneous recovery usually occurs in 1-3 years, it may, however, produce crippling deformities.

With treatment the lepromatous type regresses slowly (over a period of 3-8 years) and recovery from the tuberculoid type is more rapid. Recrudescences are always possible, and it may be safe to assume that the bacilli are never eradicated. Deformities persist, however, after complete recovery, and may markedly interfere with function and appearance.

Cochrane, R.G.: A critical appraisal of the present position of leprosy. *Internat. Rev. Trop. Med.* 1:1-42, 1961.

Doull, J.A.: Current status of the therapy of leprosy. *J.A.M.A.* 173:363-73, 1960

## CHANCROID

Chancroid is an acute, localized, often autoinoculable venereal disease caused by the fine, short, round-ended gram-negative bacillus, *Hemophilus ducreyi*. Infection occurs by contact with infected material during intercourse, although nonvenereal inoculation has occurred in medical personnel through contact with chancroid patients. The incubation period is 3-5 days.

The initial lesion at the site of inoculation is a macule or vesicopustule which soon breaks down to form a sharply circumscribed, tender ulcer with a necrotic base, surrounding erythema and undermined edges. Multiple lesions may develop by auto-inoculation. In over half of cases inguinal adenitis develops 10-20 days after disappearance of the primary lesion. The adenitis is usually unilateral and consists of tender fused nodes of moderate size with overlying erythema. The node mass softens, becomes fluctuant, and may rupture spontane-

ously. With lymph node involvement fever, chills, and malaise may occur.

The organism may be recovered by culture from the ulcer base or lymph nodes, or may be identified by staining the infectious material. The chancroid skin test (of limited value) usually becomes positive 8-25 days after the appearance of the primary lesion and probably remains positive for life. Because 12-15% of primary lesions represent mixed syphills-chancroid infection, dark-field examination should be done on all chancroid lesions.

Balanitis, phimosis, and paraphimosis are frequent complications. Infection of the ulcer with fusiform-spirochete organisms is not uncommon. A serpiginous type which spreads to the groin and thighs may occur.

Sulfonamides and tetracyclines are equally effective. Give sulfadiazine or sulfisoxazole (Gantisin®), 1 Gm. q i d for one week, or one of the tetracyclines, 0.5 Gm. every 6 hours for 5-7 days. Careful cleansing of ulcerations with soap and water b.i.d. (after the diagnosis has been made) is the only local treatment usually required. When the lesions fail to heal promptly, soaks or compresses of 1:10,000 potassium permanganate solution may be necessary. Fluctuant buboes may be aspirated with a large No. 16 needle as indicated. Warm compresses or a hot-water bottle may be applied to the groin for comfort and to hasten fluctuation or regression of buboes.

Chancroid usually responds well to treatment. Even without treatment it usually is self-limited, although the serpiginous type may persist for years.

Hamilton, I.G. Chancroid in the male. *Practitioner* 179 196-9, 1957.

## GONORRHEA

### Essentials of Diagnosis

- Purulent urethral discharge with meatal irritation and burning occurs 4-10 days after exposure
- Other urogenital structures are frequently involved later (prostate, Bartholin's and Skene's glands, vagina, cervix, uterus, and tubes)
- Pelvic peritonitis occurs occasionally in females (pelvic inflammatory disease or "PID")
- Systemic involvement is possible (arthritis, pleuritis, myositis, meningitis, endocarditis)
- Gram-negative intracellular diplococci may be seen on a smear of exudate, or may be cultured

Distinguish from nonspecific urethritis and prostatitis, *Trichomonas* and *Candida* infections, other causes of peritonitis, and other specific causes of urethritis, acute cystitis, arthritis, meningitis, endocarditis, and pleuritis

### General Considerations.

Gonorrhea is an infectious disease caused by the gram-negative intracellular diplococcus *Neisseria gonorrhoeae*. Infection usually involves the mucous membrane of the genitourinary tract and is most frequently acquired in adults by sexual intercourse. Infection may also occur by contact with contaminated material, e.g., instruments, wash-cloths, and bath water, especially in female infants and prepuberal children. The organism is destroyed promptly on drying or at temperatures over 41°C (106°F), but it may remain viable for days in a moist environment and especially if refrigerated. The incubation period is 4-10 days.

### Clinical Findings

#### A. Symptoms and Signs:

1. Men - Acute anterior urethritis is usually the first manifestation. There is a scant serous to milky urethral discharge associated with an inflamed meatal orifice and meatal burning, especially on urination. The entire urethra then becomes inflamed, the discharge thickens and becomes yellow and more profuse, and may be blood-tinged (see also Complications, below).

2. Women - Infection often is asymptomatic, but there is usually a purulent urethral discharge, in many cases evident only on "milk-ing" the urethra. Dysuria, frequency, urgency,

and nocturia occur, especially in first infections. The meatus may be red and swollen. Vaginitis, cervicitis, and inflammation of Bartholin's and Skene's glands are common.

3. Infants and prepuberal children - In children the same symptoms and signs are present but the onset is more acute, the course is more rapid, and the effects of the disease are more severe.

**B. Laboratory Findings.** Typical gram-negative intracellular diplococci are usually found in a thin smear of the urethral discharge or of material obtained from the cervix or from Bartholin's or Skene's glands. A two-glass urinary test may be of aid, since in very few other disorders is the first glass cloudy and the second glass clear. The spun sediment of the first glass may be used for identifying the organism when urethral discharge is scanty or absent. The organism may also be grown and identified on chocolate agar at reduced oxygen tension. A complement fixation test may be positive several weeks after initial infection, but this test is not reliable and is rarely used. The fluorescent antibody test may be performed directly on the exudate on a slide or on a culture slant.

### Complications

In men, direct extension of the infection into the posterior urethra, prostate, and epididymis may occur in neglected infections and with inadequate treatment. Trigonitis may occur, but cystitis is rare. Stricture of the urethra may also accompany gonorrhea. A refractory urethritis and prostatitis may persist after apparent bacteriologic "cure."

In women, local complications include Bartholin's gland abscess and chronic infection of Skene's glands. There may be extension of the infection into the endocervix, uterus, and tubes and into the surrounding pelvic structures, causing fever, chills, lower abdominal pains, and findings similar to those of acute appendicitis. Sterility due to scarring of the tubes may result.

In either sex systemic complications may occur as a result of septicemic spread, causing arthritis, myositis, pleuritis, meningitis, and endocarditis, other than arthritis these complications are uncommon. Arthritis usually involves several joints at first but ultimately only one or two, and often is associated with iritis or iridocyclitis. Gonococcal proctitis may occur in either sex.

### Treatment.

Penicillin, streptomycin, tetracyclines, and the sulfonamides are all effective, although penicillin is usually the drug of choice.

**A Acute or Chronic Uncomplicated Urethritis (Male or Female)** Note: Local treatment (irrigations, manipulations and instillations) is contraindicated

1 Penicillin therapy - Several effective techniques are available. Always draw a preliminary blood specimen for STS and examine the patient for evidence of syphilis. Give procaine penicillin G, 600 000 units I M on 2 successive days

2 Alternate therapy - If coincidental exposure to syphilis is suspected give benzathine penicillin G, 600 000 units I M daily for 10 days. If the patient is allergic to penicillin give one of the tetracyclines 1 Gm orally stat and then 0.5 Gm at 6 hour intervals for 4-6 doses

3 Follow-up - Examine the patient once a week for at least 3 weeks for evidence of urethral discharge, chancre or rash. Examine a stained smear and if possible culture any inflammatory exudate once a week. Avoid prostatic massage, urethral swabs or instrumentation as a means of obtaining material for examination in acute cases. Take a blood sample for STS and examine for clinical evidence of syphilis at the end of the third week and again at 3, 6, 12 and 24 months

4 Re-treatment of penicillin failures (suspect other etiology) - If any of the weekly checks shows bacteriologic evidence of persistent gonorrheal infection repeat penicillin treatment as above. If urologic complications can be reasonably excluded give increased doses of penicillin streptomycin sulfate 0.3-0.5 Gm I M (single dose) or tetracyclines 1 Gm orally stat and then 0.5 Gm at 6-hour intervals for 4-6 doses or 1 Gm orally stat and then 1 Gm repeated in 6 hours

5 Persistent failures - 'Treatment failures' are often reinfections. This is due in part to the fact that the public has come to believe that penicillin has removed the danger from gonorrheal infection. Promiscuous patients must be warned against this error

**B Acute and Chronic Prostatitis** Treat as above. Hot sitz baths and alkalinization of the urine may provide symptomatic relief

**C Acute Epididymitis** Treat as above and give bed rest, cold compresses to scrotal region, analgesics as necessary and a scrotal supporter for the ambulatory phase of convalescence

**D Pelvic Inflammatory Disease (Acute Gonococcal Salpingitis)**

1 Acute - Place the patient at absolute bed rest, and withhold douches and unnecessary manipulation during the acute phase

Examine carefully for clinical evidence of syphilis and draw blood for STS. Give procaine penicillin G 600,000 units I M daily for 5-10 days. If fever and other symptoms disappear, keep the patient at bed rest until WBC and sedimentation rate become normal (may take a month or more). Observe her during and following the next menstrual period for pain and changes in pelvic examination. If she remains well discharge her to home care on the convalescent program outlined below

If symptoms, fever, leukocytosis, increased sedimentation rate persist or if the vaginal smear remains positive - or if symptoms and signs recur at the time of menses administer a second course of penicillin

If the patient fails to respond to 2 courses of penicillin therapy give one of the tetracyclines 1 Gm orally stat and then 0.5 Gm at 6 hour intervals for 4-6 doses

After the patient is discharged from the hospital she should lead a sedentary life for at least 6 weeks and should abstain from sexual intercourse until signs and symptoms have completely cleared (usually takes about 6-8 weeks). Prescribe prolonged douches of warm tsp water using 1-2 gallons and administering slowly and gently (in the bathtub) over a 15-20 minute period once or twice daily

2 Subacute (or acute exacerbation of chronic form) - Prescribe absolute bed rest until the signs and symptoms have cleared and prolonged douching as above. Penicillin (as above) is much less effective in this phase of the disease but a trial of therapy is warranted

3 Chronic (gonococcal salpingitis) - Prescribe bed rest during acute exacerbations. Penicillin and other antibiotics are usually ineffective but should be tried. A course of pelvic diathermy treatments may be of value. Surgical procedures (upon a gynecologist's advice) may be indicated but are not uniformly satisfactory

## Prognosis

Gonorrhea responds well to chemotherapy but late manifestations of the disease (salpingitis, epididymitis, urethral stricture and Bartholin's gland abscess) cause damage (sterility, upper urinary tract dilatation and persistent sterile abscess) which requires separate treatment and correction

About 3% of gonorrhea patients acquire syphilis at the same exposure and should therefore have follow up blood testing

Simpson W G, & W J Brown Current status of the diagnosis and management of gonorrhea J A M A 182 63-66 1962

## GRANULOMA INGUINALE

Granuloma inguinale is a chronic, relapsing, granulomatous anogenital infection due to *Donovania granulomatis* which is auto-inoculable but only slightly contagious. In the United States it occurs predominantly in Negroes. *D. granulomatis*, a pleomorphic rod 1-2  $\mu$  long, occurs intracellularly, singly or in clusters, and is difficult to find. The pathognomonic cell, found in tissue scrapings or sections, is large (25-90  $\mu$ ) and contains intracytoplasmic cysts filled with bodies (Donovan bodies) which stain deeply with Wright's stain.

The incubation period is 8-12 weeks.

The onset is insidious. The lesions tend to be singular, on the skin or mucous membranes of the genitalia or perineal area. They are relatively painless infiltrated nodules which soon slough. A shallow, sharply demarcated ulcer forms, with a beefy red friable base of granulation tissue. The lesion spreads by contiguity. The advancing border has a characteristic rolled edge of granulation tissue. Large ulcerations which advance up onto the lower abdomen and thighs are not uncommon. Scar formation and healing may occur along one border while the opposite border advances. The process may become indolent and stationary.

The characteristic Donovan bodies are found in scrapings from the ulcer base or on histologic sections. The microorganism may also be cultured on special media. A complement fixation test has been developed but is not widely available for clinical use.

Superinfection with spirochete-fusiform organisms is not uncommon. The ulcer then becomes purulent, painful, foul-smelling and extremely difficult to treat. Other venereal diseases may coexist. Rare complications include superimposed malignancy and secondary elephantoid swelling of the genitalia.

Tetracyclines and chloramphenicol (Chloromycetin<sup>®</sup>) (caution) are both effective in doses of 1 Gm. daily for 1-2 weeks. Streptomycin is also effective but is more toxic. The dose is 1 Gm. i.M. daily until the lesion is healed (10 or more days). Recent evidence indicates that triacetyleandomycin is now the drug of choice. Watch for liver damage with prolonged use.

With antimicrobial therapy, most cases can be cured. In resistant or untreated cases massive extension of the lesion may occur, with resulting anemia, cachexia, and death.

Greenblatt, R.B., Dienst, R.B., & K.R.

Baldwin. Lymphogranuloma venereum and granuloma inguinale. *M. Clin. North America* 43 1493-1506, 1959.

BARTONELLOSIS  
(Oroya Fever, Carrion's Disease)

Bartonellosis, an acute or chronic infection which occurs in the high Andean valleys of Colombia, Ecuador, and Peru, is caused by a gram-negative, very pleomorphic organism (*Bartonella bacilliformis*) which is transmitted to man by the bite of *Phlebotomus*. The organism is parasitic in man in red cells and cells of the reticuloendothelial system. The initial febrile stage (Oroya fever) is not always distinctive, and is characterized by intermittent or remittent fever, malaise, headache, and bone and joint pains. The disease becomes more apparent with the rapid progression of severe megaloblastic anemia, hemorrhagic lymph nodes, and hepatosplenomegaly. Masses of organisms fill the cytoplasm of vascular endothelial cells, resulting in occlusion and thrombosis. In favorable cases Oroya fever lasts 2-6 weeks and subsides. In those who survive, the eruptive stage of the disease (verruca peruana) commonly begins 2-8 weeks later. Verruga may also appear in the apparent absence of Oroya fever, possibly because of a mild, subclinical first stage. Multiple muliary and nodular hemangiomas appear in crops, particularly on the face and limbs. The lesions bleed easily, sometimes ulcerate usually persist for 1-12 months, finally heal without scar formation, and produce little systemic reaction. In early Oroya fever, the organisms are best demonstrated by blood culture. Later, *Bartonella* organisms appear in red cells in large numbers. The severe macrocytic, usually hypochromic anemia (hemoglobin as low as 3-5 Gm.) of Oroya fever is accompanied by slight jaundice, marked reticulocytosis, and numerous megaloblasts and normoblasts in verrugous lesions. The organisms may be demonstrated in endothelial cells. Chloramphenicol, penicillin, streptomycin, or tetracyclines in large doses have been effective in overcoming the infection and reducing the mortality rate. Transfusion may be necessary if the anemia is severe.

## ANTI-INFECTIVE CHEMOTHERAPEUTIC & ANTIBIOTIC AGENTS

Sulfonamides, antibiotics, aminosalicylic acid, and isoniazid are used for the treatment of bacterial and rickettsial infections, for the treatment or prevention of secondary bacterial infections, in virus diseases, and for prophylaxis against streptococcal infections in patients with valvular heart disease (to prevent subacute bacterial endocarditis)

### Precautions in the Use of Chemotherapeutic Agents

- (1) Etiologic diagnosis is of paramount importance
- (2) Indiscriminate use may lead to serious toxic reactions
- (3) Insufficient dosage or unnecessary administration for minor illnesses may permit the emergence of resistant strains
- (4) Combinations of chemotherapeutic agents are usually inadvisable except (1) in multiple infections, (2) under special circumstances where synergistic action can be demonstrated, or (3) where development of resistant organisms should be delayed
- (5) Topical administration (especially penicillin and sulfonamides) may sensitize the patient so that a severe hypersensitivity reaction may occur upon later systemic use

### CHOICE OF ANTIBIOTICS IN BACTERIAL INFECTIONS (See table on p. 687.)

The choice of antimicrobial agents in the treatment of bacterial infections may be made in one of 3 ways

- (1) The clinical appearance may be so characteristic of a given etiologic agent that specific antimicrobial therapy can be chosen without bacteriologic examinations (E.g., meningococcal meningitis, acute gonorrhea, pneumococcal lobar pneumonia)
- (2) The clinical appearance may be compatible with a variety of etiologic organisms, in which case it is necessary to identify the specific organism by smear, culture, or other means. When the organism has been identified the antimicrobial drug of choice can usually be selected on the basis of clinical experience (E.g., penicillin for streptococcal infections,

chloramphenicol for salmonella enteritis, sulfonamides for meningococcemia)

(3) If the drug of choice for an identified organism is not known (due to the variability of response to antibiotics on the part of some organisms, e.g., staphylococci, coliform bacilli) - or if the organism itself is not known but can be isolated from clinical specimens - antibiotic sensitivity tests (see below) are required to determine which of several available antimicrobial agents is likely to have a bacteriostatic or bactericidal effect

### Antibiotic Sensitivity Testing

The principles of antibiotic sensitivity testing are outlined below. However, the immediate clinical situation must be borne in mind in deciding whether to wait for the results before proceeding with antimicrobial therapy. In most instances empiric therapy based on a reasoned assumption of the etiologic agent may be begun without sensitivity tests. In severe infections treatment should be begun and later altered if indicated by sensitivity tests. Tests should be performed in bacterial endocarditis, recurrent infections (especially of the urinary tract) and infections due to organisms likely to exhibit considerable strain variation in sensitivity.

**A. Plate Test** Inoculate a culture plate heavily with the clinical specimen (e.g., urine, pus, throat swab) or with a pure culture and wait a few minutes until the plate is dry. Place small filter paper disks saturated with various antibiotics on the plate 2-3 cm apart. Incubate overnight. Drugs which fail to give zones of inhibition are not likely to be clinically useful against the test organism. Note: This is a crude, rapid test which does not always correlate well with the results of tube sensitivity tests or with clinical response.

**B. Tube Test** This test measures more exactly the concentration of an antibiotic necessary to inhibit growth of a standardized inoculum under defined conditions. A series of broth tubes containing graduated amounts of an antibiotic is inoculated with a dilution of fresh broth culture of the test organism. After incubation, the tubes are examined for turbidity. The end point is considered to be that concentration of antibiotic contained in the last tube remaining clear. Upon this basis a rough estimate of the *in vivo* dose necessary to inhibit growth of the test organism can be arrived at. In addition, bactericidal effect may be determined by the tube dilution method.

## SULFONAMIDE DRUGS

The sulfonamide drugs are derivatives of sulfanilamide. The newer derivatives have wider antibacterial spectra and more desirable pharmacologic properties than the older sulfonamides. Since the activity of any sulfonamide compound may be predicted on the basis of certain physicochemical principles, it is evident that maximal antibacterial effectiveness has been approximated by sulfadiazine, sulfamerazine, sulfamethazine and sulfisoxazole (Gantrisin®), and the use of the older sulfonamides is rarely, if ever, warranted. Sulfamethoxyypyridazine (Kynex®, Midicel®) and sulfadimethoxine (Madrison®) appear to be effective at lower, less frequent doses, but they apparently are more toxic.

### Indications & Antimicrobial Spectrum. (See table on p. 655.)

The sulfonamide drugs have a wide but still limited range of activity against pathogenic agents. At the present time the sulfonamides are the therapeutic agents of choice in meningococcal infections (*Neisseria meningitidis*) and trachoma.

A. Except for meningococcal infection, the sulfonamides should be used as an alternative or in addition to one of the antibiotics against infections of known susceptibility.

B. Glucosulfone sodium (Promin®) and sulfoxone sodium (Diasone®) are related to the sulfonamide group of drugs and show promise within a limited area, they are usually used in addition to other agents in the treatment of *Mycobacterium leprae* infections.

### Pharmacologic Properties.

The sulfonamides exert a bacteriostatic effect by competing with the structurally similar natural substrate, para-aminobenzoic acid, which is necessary for the enzymatic synthesis of folic acid by bacteria. Bacterial resistance to the sulfonamides may be acquired by exposure to low concentrations.

All of the sulfonamides except sulfasuxidine, sulfaguanidine, and sulfathalidine are readily absorbed from the gastrointestinal tract and reach peak serum concentrations within a few hours. The sulfonamides diffuse readily into body fluids and exudates and appear in the CSF in about one-half the serum concentration. A varying amount is acetylated by the liver or bound to plasma protein and thus inactivated.

Excretion is principally by the kidney.

The rate of excretion varies from rapid (sulfadiazine) to very slow (sulfamethoxyypyridazine, sulfadimethoxine). Sulfadiazine, sulfathiazole, and sulfamerazine are more soluble in an alkaline urine. The likelihood of precipitation of these drugs in the urine is reduced by giving fractional doses of two or more sulfonamides.

### Blood Levels.

Under most circumstances effective blood levels will be attained by following standard dosage recommendations. Insufficient blood levels may be followed by development of sulfonamide resistance by the infecting organism. Since urine concentrations are 10-20 times that of the blood, the dosage in urinary tract infections unaccompanied by marked tissue invasion or bacteremia may be reduced.

Blood levels of sulfonamides should be determined under the following circumstances: Repeated parenteral administration, lack of expected therapeutic effect, unusually high doses, and if renal insufficiency is suspected or known.

The optimal blood level of sulfadiazine is 8-15 mg / 100 ml, of sulfamerazine, 8-15 mg / 100 ml.

### Dosages & Routes of Administration.

A Oral. See table on p. 655.

B I M . I V

1 Adults - The initial dose is 3-5 Gm of any sulfonamide (sodium salt) except sulfanilamide. This is followed by 2-3 Gm every 6-12 hours. (The optimal interval is determined by blood level just before the second dose and occasionally thereafter.) The diluent may be physiologic saline solution, Ringer's injection, sixth-molar sodium lactate solution, or Ringer's lactate injection. Ideally, the concentration should be about 0.5% but concentrations up to 5% may be used.

2 Children - As in adults. Give an initial dose of 0.065 to 0.11 Gm / Kg. of any of the sulfonamides except sulfanilamide, followed by 0.033-0.066 Gm / Kg. every 6-12 hours.

### Toxicity & Management

A Toxic Reactions

1 Mild - Continue therapy, if necessary. Symptoms and signs include nausea, vomiting, headache, dizziness, crystalluria.

2 Moderate - Stop therapy unless continuation is essential to life. Symptoms and signs include fever, rash, stomatitis, conjunctivitis, arthritis, diarrhea, microhematuria, and psychosis.

3. Severe - Stop therapy and force fluids (unless oliguria is present). Symptoms and



## Oral Sulfonamides Adult &amp; Pediatric Dosage Schedules

Indications & Preparations	Adult Dosage	Pediatric Dosage
<b>Most Infections</b>		
Initial dose One of the sulfonamides or sulfonamide mixture	2-4 Gm	20 mg/lb
<b>Maintenance</b>		
Sulfadiazine and sulfamerazine	0.5 Gm $\overline{aa}$ q 6 hours	5 mg/lb $\overline{aa}$ q 4 hours
or Sulfisoxazole	1 Gm q 6 hours	10 mg/lb q 4-6 hours
or Sulfamerazine, sulfadiazine and sulfamethazine	0.3 Gm $\overline{aa}$ q 4-6 hours	3 mg/lb $\overline{aa}$ q 4 hours
or Sulfadiazine	1 Gm q 4-6 hours	10 mg/lb q 4-6 hours
or Sulfamerazine	1 Gm q 6-8 hours	10 mg/lb q 6-8 hours
or Sulfamethoxyypyridazine or sulfadimethoxine	1 Gm daily	10 mg/lb daily
<b>Urinary Tract Infections</b>		
One of the sulfonamides or sulfonamide mixture	0.5-1 Gm q 4-8 hours	5-10 mg/lb q 4-6 hours
<b>Prophylaxis of Streptococcal Infections</b>		
One of the sulfonamides or sulfonamide mixture	0.5 Gm b i d	5 mg/lb b i d
<b>Intestinal Infections</b>		
Sulfaguanidine or succinylsulfathiazole	50 mg/lb stat then 25 mg/lb q 4 hours	

signs include granulocytopenia, hemolytic anemias, aplastic anemia, thrombocytopenia, hepatitis, exfoliative dermatitis, severe hematuria, oliguria, and a leukemoid reaction.

**B Allergic Reactions** A considerable percentage of individuals who have previously received sulfonamides, especially for more than 7 days, become sensitized and may develop immediate and severe reactions on re-administration. Fever, angioneurotic edema, urticarial and other rashes, and periarteritis nodosa may occur.

A history of previous administration should be obtained. Cross sensitivity to various sulfonamides may exist. Severe symptoms may be avoided by giving a test dose of 0.5 Gm and observing for 6 hours.

### C Precautions

1. Hemoglobin and WBC should be determined at frequent intervals. A differential count should be made if the WBC is less than 6000. Discontinue sulfonamides if the granulocyte count is less than 50%.

2. A fresh urine specimen should be examined daily for pH (use nitrazine paper) and sediment. Increase alkali (sodium bicarbonate) if the pH is less than 7.0 and discontinue

the drug if red blood cells are found in the urine. Give adequate fluids to increase urine output to at least 1500 ml/day if urine output falls or if crystalluria occurs (must be examined for in a fresh specimen).

3. Observe the patient daily for drug fever, rash, jaundice, nausea, and vomiting and other manifestations of toxicity.

### Contraindications to Sulfonamides

Do not give sulfonamides to a patient with a history of a severe reaction to any of these drugs. Patients with renal insufficiency may be given very small doses with caution. Patients with liver damage may be given sulfonamides cautiously but only if essential.

### AMINOSALICYLIC ACID (PAS)

Aminosalicylic acid (PAS) and its sodium salt have been found to exert considerable tuberculostatic activity. Tubercle bacilli resistant to streptomycin may be susceptible to PAS and vice versa. The simultaneous administration of PAS and streptomycin delays

the emergence of streptomycin-resistant strains. In addition to its bacteriostatic effect, PAS also exerts an antipyretic activity.

PAS is absorbed readily from the gastrointestinal tract. Peak serum concentrations are reached in 30-60 minutes, and minimum levels are again reached in 4 hours. PAS may also be administered I V.

#### Dosages & Routes of Administration

A Oral 3-4 Gm every 6 hours

B 15 Gm in 3% solution given in 2 doses 4 hours apart. Five mg of heparin should be added to each liter.

#### Toxicity

Nausea, vomiting, diarrhea, drug fever, dermatitis, crystalluria, hematuria and hypoprothrombinemia may be observed. Gastrointestinal symptoms may apparently be avoided by parenteral administration of sodium PAS. Anaphylactoid reaction may occur on readministration to sensitized persons.

### ISONIAZID (INH)

Isoniazid (INH) and related compounds possess considerable tuberculostatic activity. Cross-resistance to streptomycin and PAS does not exist. Bacterial resistance to INH develops rapidly. INH is readily absorbed from the gastrointestinal tract and distributed throughout the body fluids, including the CSF.

#### Dosages & Routes of Administration

Give orally, 5-10 mg /Kg /day in 2-3 doses. Ten mg /Kg should be given daily in tuberculous meningitis.

#### Toxicity

Manifestations of isoniazid toxicity are constipation, dysuria, hyperreflexia, postural hypotension and dizziness, eosinophilia, alight anemia, occasional casts and traces of protein in the urine, and reducing substances in the urine. High doses may produce pyridoxine deficiency unless supplementary pyridoxine is administered.

### PENICILLIN

Penicillin is prepared from the cultural products of the molds *Penicillium notatum*

and *Penicillium chrysogenum*. The commercially available preparations are crystalline sodium, calcium, potassium, and procaine salts of penicillin. Synthetic penicillins such as methicillin (Staphicillin<sup>®</sup>) and oxacillin (Prostaphlin<sup>®</sup>) are available which have the advantage of being resistant to the action of penicillinase.

The Oxford and International units of penicillin are measured in comparison to the bacterial inhibitory power of a standard penicillin. Crystalline sodium penicillin contains about 1500 units/mg. Dried crystalline penicillin retains its potency indefinitely, but watery solutions may deteriorate, especially when not refrigerated.

#### Indications & Antimicrobial Spectrum. (See table on p. 657.)

Penicillin exerts bacteriostatic and bactericidal effects against a wide variety of pathogenic agents, but the susceptibility of these agents to penicillin may vary considerably. Clinical response of infections may be predicted with fair accuracy by means of in vitro sensitivity tests of the infecting organism. In vitro tests should be performed when the anticipated therapeutic response does not occur, or when treating infections due to organisms such as staphylococci or *Streptococcus faecalis*, many strains of which are naturally resistant to penicillin.

Penicillin is indicated when infection with an organism known to be generally susceptible to penicillin is diagnosed or presumed. Hence one treats a specific infection, not a disease, e.g., pneumococcal pneumonia, not "pneumonia", streptococcal pharyngitis, not "acute pharyngitis". For specific indications, see the disease in question.

#### Mode of Action; Resistance.

Penicillin is both bacteriostatic and bactericidal. Its exact mode of action is not known, but it apparently interferes with cell wall synthesis.

Certain organisms produce penicillinase, which inhibits penicillin G activity. This occurs naturally, as in the case of *E. coli* and some strains of staphylococci. Susceptible organisms existing in sublethal concentrations of penicillin may acquire resistance. Mutants of naturally resistant organisms survive and multiply while the susceptible organisms are destroyed. Acquired penicillin resistance is not commonly encountered clinically. The "hospital staphylococcus" is inherently resistant because of its ability to produce penicillinase.

**Absorption, Distribution, Excretion.**

**A. Absorption:** Penicillin in aqueous solution is rapidly absorbed when administered I.V. or I.M. and somewhat more slowly absorbed after subcutaneous injection. The peak concentration in the blood is reached immediately after I.V. injection and within one hour after I.M. injection. Blood levels persist for 2-3 hours after doses of less than 50,000 units I.M. and somewhat longer with larger doses. Penicillin procaine suspensions produce measurable serum concentrations for 12-48 hours. Benzathine penicillin (Bicillin®) may produce measurable serum concentrations for one month after injection of 600,000-1,200,000 units. With all repository forms, maximum serum concentrations tend to be lower than with aqueous solutions and so are not appropriate where high serum concentrations are desirable. Penicillin, while not absorbed from the stomach, is absorbed readily from the small intestine. Approximately 5 times the I.M. dose must be given orally to produce comparable blood levels. Antacids and buffers tend to decrease the destructive effect of gastric juices, and absorption is best when the stomach is empty. Penicillin V and phenethicillin are not destroyed by gastric acid. Penicillin is poorly absorbed from the rectum and inconsistently absorbed from the vagina. The concentration of penicillin in serum and other body fluids may be measured by various bio-assay methods.

**B. Distribution:** Penicillin is distributed throughout the body fluids but penetrates the joints, pleura, peritoneum, and subarachnoid spaces irregularly. Penetration is more likely to occur if inflammation exists. Penicillin persists in the tissues for a considerable time after it has disappeared from the blood, hence continuous blood levels are not necessary in most infections. Organisms do not multiply for a considerable time after exposure to penicillin.

**C. Excretion:** Penicillin is excreted principally in the urine. Eighty percent of urinary excretion is tubular, and excretion may be partly blocked with such agents as caronamide, para-aminohippuric acid, iodo-pyruvate (Diodrast®), and probenecid (Benemid®).

**Dosages & Routes of Administration.**

**A. Intermittent I.M.:** Penicillin in aqueous solution in doses of 5000 to several million units every 3 hours I.M. is the method of choice in some severe acute infections. In many infections equally good results may be obtained by administration of 100,000-300,000 units every 12 hours I.M. injections of

300,000-600,000 units of penicillin procaine I.M. may be given every 6-24 hours. Benzathine penicillin, 0.6-1.2 million units, produces measurable serum concentrations for one month and is ideally suited for prophylactic use. These preparations are highly satisfactory except in the most severe acute infections. Methicillin should be given in doses of 2-3 Gm. every 6 hours I.M.

**B. Continuous I.M. and Continuous I.V.** Where very high doses of penicillin are necessary in the treatment of infections due to resistant organisms, administration by continuous drip is often advantageous. Many millions of units, dissolved in 1-2 L. of physiologic saline or 5% glucose solution, may be given by indwelling needle or catheter in 24 hours. Methicillin may be given by continuous I.V. drip, 8-12 Gm /24 hours. The I.M. site should be changed as frequently as irritation occurs. Thrombophlebitis as a complication of I.V. administration may be avoided by changing the vein used or by addition of 10 mg heparin sodium to the solution.

**C. Oral:** Penicillin may be given orally in all but the severest of infections, or oral medication may be substituted for parenteral after initial response to treatment. Doses of 100,000 units every 3 hours to 300,000 units every 6-8 hours may be given. Penicillin V may be given in a dose of 125-250 mg every 8 hours. Phenethicillin is given orally, 250 mg every 6 hours. Oxacillin is given orally, 500 mg every 6 hours.

**D. Topical:**

**1. Aerosol:** 50,000-100,000 units may be aerosolized from 3-8 times a day. A solution containing 50,000 units/0.5 ml may be nebulized with a Vaponephrin® or De Vilbiss No. 40® nebulizer. Forced, deep inhalation followed by retention of the inspired penicillin as long as possible should be ensured. Hand pumping or compressed gas fed through a "Y" tube may be used to nebulize the solution. Although local effect in the respiratory passages for the treatment of bronchiectasis, chronic bronchitis, and similar disorders, is usually objective, appreciable blood concentrations of penicillin frequently result. Sensitization occurs commonly.

**2. Intrathecal:** Although penicillin may penetrate the subarachnoid space after I.M. injection, this phenomenon is inconstant and may be delayed. Therefore, in severe cases of meningitis due to susceptible organisms, 10,000 units of penicillin dissolved in 10 ml. of physiologic saline should be administered once a day until the CSF glucose content becomes

normal Penicillin should also be given I M

3 Intrapleural intra articular Ten thousand to 200 000 units of penicillin may be introduced into joint or pleural spaces infected by susceptible organisms daily or every other day following aspiration

4 Wounds and skin Solutions of penicillin containing 200 1000 units/ml may be used as a wet dressing in infected wounds Penicillin is of no value as an irrigating solution because of the necessity of prolonged contact to produce antibacterial effect

### Toxicity

Since the purification of penicillin true toxic reactions are unknown Sensitization may be pre existing or induced Fever and rashes especially urticarial may appear during the course of penicillin administration or as long as several weeks later This may exactly mimic serum sickness True idiosyncrasy to penicillin is rare Positive intra dermal tests to weak penicillin solutions may be observed Desensitization may be attempted Patients known to be sensitive to penicillin may be treated with penicillin O (Cer-O Cillin® or Depo Cer O Cillin®) or erythromycin which may be substituted for aqueous or procaine penicillin Cross sensitivity occurs occasionally and should be guarded against

### ERYTHROMYCIN

(Erythrocin®, Ilotycin®, Ilosone®)

Erythromycin is a medium spectrum antibiotic derived from *Streptomyces erythraeus* It may be bactericidal or bacteriostatic depending upon the susceptibility of the bacteria Resistance to erythromycin (most notably by staphylococci) may develop rapidly under certain circumstances For this reason erythromycin should not be used alone in serious staphylococcal infections

Erythromycin propionyl ester (Ilosone®) provides higher levels than other preparations and is preferable for use over short periods

Indications & Antimicrobial Spectrum (See table on p 667)

Erythromycin is active against most strains of gram positive cocci gram negative cocci *Corynebacterium diphtheriae* *Hemophilus influenzae* *Haemophilus pertussis* and *Brucella* Activity has also been shown against the viruses of lymphopathia venereum and psittacosis and the rickettsia of typhus Erythromycin may be used in infections due to these organisms as

an alternative to penicillin and other antibiotics

### Dosages & Routes of Administration

A Oral 0.2 to 0.5 Gm every 6 hours

B I V 0.5 Gm every 12 hours

### Toxicity

Nausea vomiting and diarrhea occur occasionally Hepatitis has followed the use of erythromycin propionyl ester lauryl sulfate for several weeks

### TRIACETYLEANDOMYCIN (TAO®)

Triacetyloleandomycin is derived from *Streptomyces antibioticus* It is principally active against gram positive cocci including many strains of staphylococci *Gonococcus meningococcus* *H. influenzae* and *Brucella* organisms are also sensitive Cross resistance with erythromycin is common Triacetyloleandomycin may be indicated in staphylococcal infections resistant to erythromycin and other antibiotics Its action is similar to that of erythromycin but it is less effective

The dosage is 0.25 to 0.5 Gm every 6 hours orally Nausea vomiting diarrhea hepatitis and skin rashes occur occasionally

### STREPTOMYCIN

Streptomycin is prepared from the cultural products of *Streptomyces griseus* Dihydro streptomycin has been used alternatively with streptomycin but is less frequently used now Vestibular damage is less frequent following dihydrostreptomycin therapy but deafness occurs more often than with streptomycin treatment One mcg equals one Waksman unit 1 Gm equals one million Waksman units

Indications & Antimicrobial Spectrum (See table on p 667)

Streptomycin is principally active against gram negative organisms but possesses significant activity against some strains of gram positive cocci Penicillin and streptomycin may exert marked synergistic activity in infections due to *Streptococcus faecalis* and streptomycin and chlortetracycline exert synergistic activity in brucellosis

The indications for streptomycin are almost entirely limited to infections due to gram-negative organisms and tuberculosis. For this reason exact etiologic diagnosis should be sought before instituting treatment. Most tubercle bacilli become streptomycin-resistant within 3 months of the beginning of treatment, although the simultaneous use of PAS or isoniazid delays this event, and one or both should always be used with streptomycin in tuberculosis.

#### Mode of Action, Resistance.

Streptomycin is both bacteriostatic and bactericidal. Its mode of action is not known. Resistant variants of organisms may multiply quickly in infections treated with streptomycin, so that further therapy with the antibiotic is useless. Streptomycin should be used only when necessary, and adequate initial dosage should be used to prevent development of drug resistance.

#### Absorption, Distribution, & Excretion

**A. Absorption:** Streptomycin is readily absorbed from the site of I. M. injection. The peak serum concentration is reached within one hour, and detectable amounts are present up to 6 hours later. It is likely that streptomycin persists longer than this in the tissues. If streptomycin is administered every 3-4 hours, gradually increasing serum levels will be noted due to slow accumulation. Administration every 6 hours is sufficient in all but the most acute infections, in which cases the drug should be given initially every 3 or 4 hours. Streptomycin is not absorbed from the gastrointestinal tract but exerts bacteriostatic activity in the lumen of the bowel.

**B. Distribution:** Streptomycin is distributed throughout the body similarly to penicillin. Penetration of the CSF is inconstant and unreliable.

**C. Excretion:** Streptomycin is excreted principally in the urine, where the concentration exceeds that in the serum.

#### Dosages & Routes of Administration.

**A. Nontuberculous Infections:** One to 5 Gm. daily may be given I. M. in divided doses every 3-6 hours. Most acute generalized infections require approximately 2-4 Gm./day. Urinary tract infections due to highly susceptible organisms may be treated with 500 mg. I. M. every 6 hours for 5 days. Streptomycin should not be used in the presence of obstruction of the urinary tract because of the near certainty of the development of resistant organisms.

**B. Meningitis:** In addition to I. M. administration, 25-50 mg. dissolved in 10 ml. of physiologic saline solution may be given intrathecally once daily until the CSF glucose content becomes normal.

**C. Bacillary Dysentery:** Streptomycin may be given orally, 0.5 Gm. every 6 hours for shigella dysentery.

**D. Tuberculosis:** One Gm. of streptomycin I. M. twice weekly, and sometimes even daily, is indicated in nondisseminated forms of tuberculosis. In acute cases of tuberculous pneumonia and miliary tuberculosis, 40 mg./Kg./day should be given. In tuberculous meningitis, 60 mg./Kg./day should be administered I. M. in addition to 2 mg./Kg./day intrathecally, if isoniazid is not used simultaneously (See Isoniazid Meningitis, p. 637.)

#### Toxicity

Painful local reactions are uncommon. Drug rashes of many sorts occur, drug fever may be observed, and slight nausea and dizziness are frequent. Eosinophilia may be noted but appears to have no significance. Cylindruria and nitrogen retention not associated with permanent renal damage have been reported. Vestibular damage, often manifested first by tinnitus and characterized by severe vertigo and ataxia, follows high or prolonged dosage. If streptomycin is discontinued immediately, recovery usually follows. If vestibular damage becomes permanent, satisfactory compensation is usually made by the patient. Deafness also may occur but it is rarer. Vestibular apparatus depression is less common with dihydrostreptomycin, but deafness may develop after treatment has been stopped. Pleocytosis, increase in protein content of the CSF, subarachnoid block, or myelitis may follow prolonged intrathecal administration of streptomycin.

#### TETRACYCLINE GROUP

(Chlortetracycline, Oxytetracycline, Tetracycline, Demethylchlortetracycline)

These chemically related drugs possess similar antimicrobial spectra and pharmacologic properties. Organisms resistant to one drug are usually resistant to the others, although significant variations occasionally occur. In general they are clinically interchangeable. They exert only bacteriostatic activity.

## 1. OXYTETRACYCLINE (Terramycin®)

Oxytetracycline (Terramycin®) is derived from *Streptomyces rimosus*

**Indications & Antimicrobial Spectrum.** (See table on p. 667.)

Oxytetracycline is a broad-spectrum antibiotic whose range of activity is similar to that of chlortetracycline. It may be used in infections due to gram-positive and gram-negative cocci, gram-positive and gram-negative rods, spirochetes, rickettsiae, and the viruses of primary atypical pneumonia, lymphopathia venereum, and psittacosis.

### Absorption & Excretion

Oxytetracycline is incompletely absorbed from the gastrointestinal tract. Satisfactory serum levels may be maintained by giving the drug every 6 hours. Excretion is principally by the kidneys. Significant amounts appear in the bile. Appearance in the CSF is delayed and irregular.

### Dosages & Routes of Administration

**A. Oral** 0.25-1 Gm. may be given orally every 6 hours.

**B. I.V.** 0.5-1 Gm. may be administered every 12 hours. Oral therapy should be used whenever possible.

**C. I.M.** The preparation for I.M. use may be given in a dose of 0.5 Gm. every 24 hours or 0.1 Gm. every 6 hours.

### Toxicity

Nausea, vomiting, diarrhea, stomatitis and dermatitis occur occasionally. Hepatitis may result from prolonged I.V. treatment at high dosage. Thrombophlebitis may result from I.V. administration. Superinfection with resistant staphylococci may occur, usually as a severe enterocolitis. This also occurs with other broad-spectrum antibiotics. Mild toxicity may be removed by reducing the oral dose or by giving the drug I.V.

## 2. CHLORTETRACYCLINE (Aureomycin®)

Chlortetracycline (Aureomycin®) is prepared from *Streptomyces aureofaciens*. It is available as the hydrochloride.

**Indications & Antimicrobial Spectrum.** (See table on p. 667.)

Chlortetracycline (Aureomycin®) is an alternative to penicillin or streptomycin in most bacterial infections. It is a broad-spectrum antibiotic with a wide therapeutic range. It is active against most gram-negative rods and gram-positive cocci, the spirochetes of leptospirosis, relapsing fever, rat-bite fever, syphilis, and yaws, and the rickettsiae of typhus, Rocky Mountain spotted fever, scrub typhus, Q fever, and rickettsialpox. It is highly active against the viruses of psittacosis, lymphopathia venereum, and one virus causing primary atypical pneumonia.

### Absorption & Excretion

Chlortetracycline is absorbed slowly from the gastrointestinal tract, peak blood concentrations are reached in 2-4 hours and persist as long as 12-24 hours, depending upon the dose. I.V. administration produces an immediate high blood concentration which drops over a period of 6-24 hours, varying with the dose. Chlortetracycline is excreted slowly by the kidney. It does not appear readily in the CSF or pleural fluid, but it is present in high concentration in the urine and stools.

### Dosages & Routes of Administration

**A. Oral** 0.25-1 Gm. orally every 6 hours appears to be adequate in most acute infections. Gastrointestinal symptoms may be minimized by administering the drug only when food is in the stomach or by simultaneously administering carboxymethylcellulose. Superinfections with yeasts in the oropharynx and perineal area may occur but are probably secondary infections of local sensitivity reactions.

**B. I.V.** Similar results may be obtained by the I.V. administration of 100 mg. every 6-8 hours or 500 mg. every 12 hours. In resistant infections, combined oral and I.V. therapy may be used.

### Toxicity

Same as that of oxytetracycline.

### 3 TETRACYCLINE

(Achromycin®, Tetracyn®, Polycycline®, Steclin®, Panmycin®)

Tetracycline is produced by removing the chlorine from chlortetracycline. It is similar to chlortetracycline and oxytetracycline but is more stable in solution than either derivative.

**Indications & Antimicrobial Spectrum.** (See table on p 667.)

Tetracycline is a broad-spectrum antibiotic whose field of activity is similar to those of chlortetracycline and oxytetracycline. Susceptibility of strains of bacteria may differ among the 3 drugs, however.

#### Absorption & Excretion

Tetracycline is absorbed and excreted similarly to chlortetracycline. It may diffuse more readily into the CSF.

#### Dosages & Routes of Administration.

A Oral 0.25-1 Gm every 6 hours

B I V 0.5-1 Gm every 12 hours

C I M 0.1 Gm every 8-12 hours

#### Toxicity

Similar to that of chlortetracycline and oxytetracyclins but significantly less frequent.

### 4 DEMETHYLCHLORTETRACYCLINE (Declomycin®)

Demethylchlortetracycline is a derivative of chlortetracycline.

#### Indications & Antimicrobial Spectrum

Similar to other members of the tetracycline group.

#### Absorption & Excretion

Demethylchlortetracycline is better absorbed and more slowly excreted than other tetracyclines. This advantage is partly lost by protein binding in the serum.

#### Dosages & Routes of Administration

Orally 150 mg every 6 hours

#### Toxicity

Similar to that of other tetracyclines. Photosensitivity may occur.

### CHLOROAMPHENICOL (Chloromycetin®)

Chloroamphenicol (Chloromycetin®) originally prepared from *Streptomyces venezuelae* is now produced synthetically.

#### Indications & Antimicrobial Spectrum (See table on p 667.)

Chloramphenicol is active against a wide range of bacteria, the rickettsiae and the viruses of lymphogranuloma venereum, psittacosis and primary atypical pneumonia. Generally speaking, it is more effective than the tetracyclines in typhoid fever, approximately equal in effect against other gram-negative organisms, spirochetes and rickettsiae. Many staphylococci remain susceptible to chloramphenicol.

#### Absorption & Excretion

Chloramphenicol is rapidly absorbed from the gastrointestinal tract, reaching a peak serum concentration within 2 hours. Absorption following rectal administration is slightly less efficient. One-half Gm may be administered I M or I V every 6 hours. Excretion is principally by the kidneys, and high concentrations are reached in the urine.

#### Dosages & Routes of Administration

A Oral Adult 0.5 Gm every 6 hours, children 40 mg /Kg /day

B Rectal (for Children) 125-150 mg /kg /day in divided doses given every 6 hours. The capsule should be punctured before insertion.

C I M and I V 500 mg every 6 hours

#### Toxicity

Nausea and vomiting, diarrhea, nervous depression, dermatitis, granulocytopenia, and aplastic anemia occur occasionally. Therefore, chloramphenicol should be used only on definite indications. Collapse may follow administration to premature infants.

### TYROTHRICIN

Tyrothricin is prepared from *Bacillus brevis*. It is used topically as an ointment or aqueous suspension. It is active only against gram-positive organisms. Because of toxic

effects on parenteral administration, its use is limited entirely to the topical treatment of infected wounds and pyoderma. Tyrothricin is also available in many proprietary lozenges, but it is not effective when used in this way.

### POLYMYXIN (Aerosporin®)

The polymyxins, of which B, D, and E have been given clinical trial, are derived from *Bacillus polymyxa* and related organisms.

#### Indications & Antimicrobial Spectrum. (See table on p. 667.)

With the exception of most strains of *Proteus vulgaris*, polymyxin is bactericidal against gram-negative rods and many strains of *Pseudomonas aeruginosa*. Polymyxin is indicated in severe systemic infections due to gram-negative rods, particularly infections due to *Pseudomonas aeruginosa* which do not respond to other forms of chemotherapy. It may be used locally in wounds infected with susceptible organisms. It may be given orally in the treatment of the shigella carrier state.

#### Absorption & Excretion

Absorption is rapid after intramuscular injection. Excretion is largely by the kidney and high concentrations are achieved in the urine. Polymyxin is not absorbed from the gastrointestinal tract, and when it is given by mouth it exhibits its principal activity in the lumen of the bowel.

#### Dosages & Routes of Administration

A I M 1.5-2.5 mg /Kg /day in 3 or 4 doses

B Oral 20 mg /Kg /day in 3 or 4 doses

C Intrathecal In meningitis 2 mg /day for small children and 5 mg /day for older children and adults in 1 ml of physiologic saline should be instilled into the subarachnoid space.

#### Toxicity

Most toxic effects occur at dosage levels over 2.5 mg /Kg /day. Proteinuria and nitrogen retention are usually reversible. Weakness, drowsiness, ataxia, numbness of the fingers and feet, impaired position sense, blurring of vision, diplopia, and nystagmus may occur. Allergic reactions, such as itchy-

ing, chilly sensations, sweating, and rashes are observed. Irritation at the site of I M injection is common.

### COLISTIMETHATE (Coly-Mycin®)

Colistimethate is derived from *Aerobacillus colistinus*. Its properties are very similar to those of polymyxin, but it is less toxic.

#### Indications & Antimicrobial Spectrum.

Colistimethate acts against many gram-negative pathogens in a bactericidal manner. It is effective against *E. coli*, *A. aerogenes*, *bruceellae* and many strains of *Pseudomonas*. It is ineffective against *Proteus*. It is indicated when bactericidal activity against susceptible organisms is required.

#### Absorption & Excretion

Colistimethate is not absorbed from the gastrointestinal tract. I M absorption is prompt. I V use is not recommended. It is excreted in the urine.

#### Dosages & Routes of Administration

Give I M 1.5-5 mg /Kg /day

#### Toxicity

Paresthesias, dizziness, drug fever, and rash. Nephrotoxicity appears less than that of polymyxin.

### BACITRACIN

Bacitracin is derived from the growth products of *Bacillus subtilis*.

#### Indications & Antimicrobial Spectrum.

Bacitracin is active against gram-positive cocci and spirochetes. Its action is principally bactericidal. Synergistic action with penicillin and other bactericidal antibiotics has been demonstrated against staphylococci and other organisms. Bacitracin is principally used topically for local infections due to susceptible organisms, but it may be used parenterally in the treatment of infections resistant to other antibiotics or in combination with other antibiotics as one of a synergistic pair.



It may be used orally in the treatment of amebic colitis. Most staphylococci are susceptible to bacitracin.

#### Dosages & Routes of Administration.

A. Topical. Solutions or ointments containing 500 units/ml

B. Oral. 40,000-120,000 units in divided doses daily for 5-20 days

C. I. M. 2500-20,000 units every 6 hours

#### Toxicity.

Proteinuria, cylindruria, and nitrogen retention commonly occur after parenteral administration.

### NEOMYCIN

Neomycin is derived from *Actinomyces fradii*.

Indications & Antimicrobial Spectrum. (See table on p. 667.)

Neomycin is most active against gram-negative rods but is also active against many strains of gram-positive cocci, particularly staphylococci, as well as gram-positive rods. Many strains of *Proteus vulgaris* are sensitive to neomycin. Its principal use is in the local treatment of infections due to susceptible organisms, but it may be used occasionally parenterally in the treatment of infections due to organisms resistant to other antibiotics or may be used as one of a synergistic pair. It may be used orally to sterilize the bowel before gastrointestinal surgery and in amebic colitis.

#### Absorption & Excretion

Neomycin is readily absorbed after I. M. injection. It is poorly absorbed from the gastrointestinal tract. It exerts its principal activity in the lumen of the bowel when given orally. Neomycin is principally excreted by the kidney and appears in the urine in high concentration.

#### Dosages & Routes of Administration.

A. Topical. Ointments containing 1000 units/Gm. or solutions containing 200 units/ml may be used locally.

B. Oral. 0.1 Gm /Kg /day in 4-6 doses

C. I. M. 15-20 mg /Kg /day in 4 doses

#### Toxicity

Renal damage is manifested by proteinuria. Nitrogen retention may occur. Deafness may follow parenteral administration.

### KANAMYCIN (Kantrex®)

Kanamycin is derived from *Streptomyces kanamyceticus*. Its antimicrobial spectrum and other properties resemble those of neomycin, i. e. it is effective against most gram-positive and gram-negative organisms, including staphylococci and *Mycobacterium tuberculosis*. It is relatively inactive against pneumococci, streptococci, and clostridia. It is generally less active than neomycin, and its indications are similar.

Kanamycin is readily absorbed after I. M. injection. It is poorly absorbed after oral administration. It appears in the CSF and bile and is excreted in the urine.

The dosage is 0.25-0.5 Gm. every 6 hours I. M. Toxicity includes kidney damage and deafness, particularly with high doses or prolonged use.

### FUMAGILLIN (Fumidil®)

Fumagillin is derived from *Aspergillus fumigatus* H-3. It is directly amebicidal and apparently is effective also against other enteric protozoa. It has been valuable in the treatment of drug-refractive amebiasis. The dosage is 30-60 mg orally daily for 10 days.

### NITROFURANTOIN (Furadantin®)

Nitrofurantoin is active against a wide variety of bacteria, both gram-positive and gram-negative. It is readily absorbed from the gastrointestinal tract and excreted in high concentrations in the urine. Serum and tissue concentrations are insignificant. It is used for the treatment of infections of the urinary tract where significant tissue invasion and bacteremia do not exist. Toxic reactions include gastrointestinal irritation and occasional skin rashes.

The dosage for adults is 100 mg orally 4 times daily, for children, 5-8 mg /Kg /day. An I. V. preparation is now available but its exact clinical indications are not yet known.

**VIOMYCIN**  
(Vinactane® Vlocin®)

Viomycin is derived from *Streptomyces* *purpureus*. It is active only against *Mycobacterium tuberculosis* including strains resistant to streptomycin, aminosalicylic acid and isoniazid. Because it is highly nephrotoxic and neurotoxic, its use is very limited. Toxic reactions include eighth nerve damage and renal insufficiency with disturbed electrolyte balance.

The dosage is 2 Gm 1 M every third day.

**NYSTATIN**  
(Mycostatin®)

Nystatin is derived from *Streptomyces noursei*. It is active against a wide variety of fungi and yeasts and is very poorly absorbed from the gastrointestinal tract, so that its activity is principally within the lumen of the bowel or wherever applied locally. Superinfection with yeasts caused by tetracycline therapy may be reduced by oral administration of nystatin. It may be used locally in yeast infections of the mouth, genitalia or skin.

The dosage is 500 000 units orally 3 times daily, 100 000 units locally as vaginal suppositories once or twice daily or as ointment (100 000 units/Gm).

**AMPHOTERICIN B**  
(Fungizone®)

Amphotericin is derived from a *Streptomyces*. It is active against a wide variety of fungi including *Candida albicans*, *Cryptococcus neoformans*, *Blastomyces dermatitidis* and *B. brasiliensis*, *Sporotrichum schenckii*, *Coccidioides immitis* and *Histoplasma capsulatum*. It is indicated in severe systemic fungal infections due to these organisms.

Amphotericin B is poorly absorbed orally and should be given I V. In coccidioidal meningitis, intrathecal therapy is probably advisable. Give 1-1.5 mg /Kg /day or every other day as a slow I V drip. It may be given intrathecally 0.5-1 mg in 10 ml of CSF every other day.

Toxicity includes chills, fever, malaise, renal damage, liver damage and thrombophlebitis.

**NOVOBIOCIN**  
(Albamycin® Cathomylin®)

Novobiocin is derived from *Streptomyces niveus*. It is a broad spectrum antibiotic which is readily absorbed from the gastrointestinal tract and achieves very high concentrations in the serum, but is largely bound to serum protein.

Novobiocin is useful in staphylococcal infections resistant to other antibiotics as well as in infections with many other bacteria and *Entamoeba histolytica*.

Drug rashes and eosinophilia are common. Resistance may develop.

The dosage is 0.25-5 Gm every 6 hours orally.

**RISTOCETIN**  
(Spontin®)

Ristocetin is derived from *Nocardia lurida*. It is active against gram positive rods and cocci, notably staphylococci and enterococci. It is indicated in severe infection with these organisms which is not susceptible to treatment with more commonly used antibiotics.

Ristocetin must be given I V. The amount to be administered should be dissolved in 30-100 ml of 5% dextrose solution and introduced over a period of 10-30 minutes into the tubing of a 5% dextrose solution as an I V drip. The dosage is 25 mg /Kg /day in 2 doses.

Toxicity includes thrombophlebitis (from slow injection), thrombocytopenia, frequent leukopenia, anemia, drug fever and drug rash.

**VANCOMYCIN**  
(Vancocin®)

Vancomycin is derived from *Streptomyces orientalis*. It is active against gram positive rods and cocci and the gonococcus. It is indicated in the treatment of infections due to these organisms, especially staphylococcal infections which do not respond to more commonly used antibiotics.

Vancomycin must be administered I V. A total daily dose of 2 Gm should be given by slow I V drip divided into 2-4 doses.

Toxicity includes thrombophlebitis, drug fever and drug rash, renal damage and deafness.

## IMMUNIZATION SCHEDULES

Biologicals for immunization purposes are gradually being modified and their schedules and methods of administration altered. The schedules and methods listed below do not apply to all preparations, follow the manufacturer's instructions which accompany the preparation.

## Children During the First Year

Either of the following schedules may be used

(1) Combined diphtheria pertussis tetanus (DPT) immunization. Give 3 injections of 0.5 ml each I M at intervals of one month starting at 1-2 months of age. A fourth dose of 0.5 ml should be given 7-12 months after the third dose. Depot triple antigens are now recommended instead of the fluid preparations. Polioomyelitis vaccine, Salk type (inactivated) 1 ml I M, may be given at the same time for a total of 3 doses. Active immunization with live oral (Sabin) vaccine should be used in place of, or in addition to Salk vaccine\*. Smallpox vaccination† may be done at any time after about one month, preferably at about 6 months of age at the time of, or following the third DPT injection.

(2) Uncombined method. Give pertussis vaccine, 3 injections of 0.5 ml each I M at

Oral Polioomyelitis Vaccine (Sabin)  
Immunization Schedules

Dose	Type	Interval From Previous Dose
<b>Infants &amp; Children</b>		
First	I	--
Second	III	6 weeks
Third	II	6 weeks
Fourth	I, II, III	6 months or longer

Adults. Type III oral vaccine should not be given to adults except to those who have not received Salk vaccine who are (1) entering hyperendemic areas or (2) during actual or imminent epidemics.

First	I	----
Second	II	4-6 weeks
Third	I & II	6 months or longer

\*Infants should begin polioomyelitis immunization between 6 weeks and 3 months of age. Immunization preferably should not be carried out during the summer months because of the likelihood of interference by enteroviruses. The individual dose of each type is 200 000-500 000 TCID<sub>50</sub> given in a simple syrup or on a sugar cube.

intervals of one month beginning at 1-2 months of age, diphtheria tetanus toxoid (DT), 3 injections of 0.5 ml I M each at intervals of one month beginning at 6 months of age with a fourth dose 7-12 months after the third and smallpox vaccination‡ at 6 months to one year of age. Repeat smallpox vaccination‡ if a "take" does not occur. Polioomyelitis vaccine, Salk type (inactivated), 1 ml I M, may be given at the same time as the pertussis vaccine. Active immunization with live oral vaccine should be used in place of, or in addition to Salk vaccine\*.

## Preschool Children Over One Year of Age

Immunize as above if no previous immunization has been given. For previously immunized children, give recall injections as follows: (1) DPT, 0.5 ml I M at 18-24 months and 4 years of age, (2) polioomyelitis (see footnote below, left).

## Children of School Age

If no previous immunization has been given, give DT, 3 injections of 0.5 ml each I M, at intervals of one month and a fourth dose 7-12 months after the third. Smallpox vaccination‡ may be done at any time in the schedule preferably at the time of or soon after the third injection of DT. For previously immunized children, give recall injections as follows: (1) Smallpox vaccination‡ at 6 years of age and then every 3-7 years or on exposures, (2) polioomyelitis (see footnote below, left), (3) DT (adult type), 0.5 ml I M at 8 years of age and repeat every 4 years.

## Adults

Adults traveling to foreign countries should obtain a list of required immunizations when applying for their passports. Those living in epidemic areas should maintain their immunization. If no previous immunization has been given, full courses are indicated as outlined above for children or according to the manufacturer's directions.

The following routines are suggested:

(1) Smallpox vaccination‡. Repeat every 3 years or on exposure.

(2) Typhoid-paratyphoid vaccine. Two injections of 0.5 ml each subcut not less than 4 weeks apart. Under ordinary circumstances, in an area of low endemicity, revaccinate not more than twice with a single injection of 0.5 ml subcut or 0.1 ml intracut administered at intervals of 4 years. In areas of high prevalence or because of other increased risk, annual single booster injections may be given 0.5 ml subcut or 0.1 ml intracut.

‡Assurance of a successful vaccination is important.

(3) Yellow fever vaccine\* (Africa and South America) 0.5 ml subcut. Reimmunization at six-year intervals is required for travel to and from yellow fever areas

(4) Typhus vaccine\* (Europe, Asia, Africa) Two injections of 0.5 ml each subcut or 1 M, not less than 4 weeks apart. Reimmunization with a single 0.5 ml dose may be required in areas where typhus is a hazard

(5) Cholera vaccine (Asia, Near East and East Indies) Two injections, 0.5 ml and 1 ml subcut or 1 M, not less than 4 weeks apart, with reimmunization (0.5 ml) every 6 months where cholera is a hazard

(6) Plague vaccine (Egypt, Asia, and East Indies) Two injections, 0.5 ml and 1 ml subcut or 1 M, not less than 4 weeks apart, with a third injection of 0.5 ml 4-6 months after the second. Reimmunization by a single injection of 0.5 ml at four- to six-month intervals may be indicated where plague is a hazard

(7) Tetanus toxoid Two injections of 0.5 ml 1 M 4-8 weeks apart with a third approximately 12 months after the second. A booster or recall dose of 0.5 ml should be given as soon as possible after injury or burn or at the time of secondary operation or manipulation of old wounds

(8) Diphtheria immunization in adults may be followed by severe local and general reactions. The best method for avoiding these reactions is to use the product labeled tetanus-diphtheria toxoids combined adsorbed (for adult use). This product has, in addition to the usual dose of tetanus toxoid, a very small amount of diphtheria toxoid, but a quantity shown to be adequate to confer immunity to diphtheria in 95% or more of American adults when given as indicated above for tetanus toxoid. This combined antigen is recommended for the immunization of adults to tetanus and diphtheria

(9) Poliomyelitis vaccine 1 ml 1 M 1 ml after one month and 1 ml after 7 months followed by a fourth injection of 1 ml one year later. Active immunization with live oral vaccine should be used in place of, or in addition to, Salk vaccine (see footnote on p. 665)

## HYPERSENSITIVITY TESTS & DESENSITIZATION

Before injecting antitoxin or similar material derived from animal sources, always perform the following tests for hypersensitivity

\*These vaccines are prepared by cultivation in eggs and should not be administered to persons with significant allergy to eggs or chicken

ty. If both tests are negative, desensitization is not necessary and a full dose of the antitoxin may be given. If one or both of the tests are positive, desensitization is necessary.

**A Intradermal Test** Inject 0.1 ml of a 1:10 dilution of the antitoxin intradermally on the flexor surface of the forearm. A large wheal and surrounding areola appearing within 30 minutes constitute a positive test.

**B Conjunctival Test** Instill one drop of a 1:10 dilution of the antitoxin into the conjunctival sac of one eye as a test dose and one drop of physiologic saline into the other eye as a control. Conjunctival redness, itching and edema appearing within 30 minutes in the test eye constitute a positive test.

## Desensitization

### A Precautionary Measures

1. An antihistaminic drug should be administered before beginning desensitization in order to lessen any reaction that might occur.

2. Epinephrine 0.5-1 ml of 1:1000 solution must be ready in a syringe for immediate administration.

**B Desensitization Method** The following plan may be used in desensitization. Give doses of antitoxin 1 M at 30-minute intervals and observe closely for reactions.

- 1st dose - 0.1 ml (1:10 dilution)
- 2nd dose - 0.2 ml (1:10 dilution)
- 3rd dose - 0.5 ml (1:10 dilution)
- 4th dose - 0.1 ml (undiluted)
- 5th dose - 0.2 ml (undiluted)
- 6th dose - 0.5 ml (undiluted)
- 7th dose - 1 ml (undiluted)
- 8th and subsequent doses - 1 ml (undiluted) every 30 minutes until the total amount of antitoxin is given

## Treatment of Reactions

A. If a mild reaction occurs, drop back to the next lower dose and continue with desensitization. If a severe reaction occurs, administer epinephrine (see below) and discontinue the antitoxin unless treatment is urgently needed. If desensitization is imperative, continue slowly, increasing the dosage of the antitoxin more gradually.

B. If manifestations of a severe reaction appear, give 0.5-1 ml of 1:1000 epinephrine subcut at once. The symptoms include urticaria, angioneurotic edema, dyspnea, coughing, choking, and shock. Observe the patient closely, and repeat epinephrine as necessary. Corticosteroids may be used (hydrocortisone 100 mg I.V.).

## Choice of Anti-infective Agents

Organism (and Gram Reaction)	Drug of First Choice	Drug of Second Choice
<i>Actinomyces</i> (+)	Penicillin plus sulfonamides	Tetracyclines
<i>Aerobacter aerogenes</i> (-)	Chloramphenicol	Neomycin
<i>Bacillus anthracis</i> (+)	Penicillin	Erythromycin
<i>Bacteroides</i> (-)	Tetracyclines	Penicillin
<i>Borrelia recurrentis</i> (-)	Tetracyclines	Penicillin
<i>Brucella</i> (-)	Tetracyclines plus streptomycin	Streptomycin plus sulfonamides
<i>Clostridia</i> (+)	Penicillin	Tetracyclines, erythromycin, sulfonamides, chloramphenicol
<i>Corynebacterium diphtheriae</i> (+)	Penicillin	Tetracyclines, erythromycin, chloramphenicol
<i>Diplococcus pneumoniae</i> (+)	Penicillin	Erythromycin, tetracyclines
<i>Donovania granulomatis</i> (-)	Tetracyclines	Chloramphenicol, streptomycin
Eaton agent	Tetracyclines	
<i>Erysipelothrix</i> (+)	Penicillin	Tetracyclines, erythromycin
<i>Escherichia coli</i> (-)	Tetracyclines	Chloramphenicol, streptomycin, neomycin
<i>Hemophilus influenzae</i> (-)	Streptomycin	Chloramphenicol plus sulfonamides
<i>Klebsiella pneumoniae</i> (-)	Tetracyclines plus streptomycin	Chloramphenicol, sulfonamides
<i>Leptospira icterohaemorrhagiae</i>	Tetracyclines	Penicillin
<i>Lymphogranuloma venereum</i> , psittacosis, and trachoma viruses	Tetracyclines	Chloramphenicol, sulfonamides
<i>Mycobacterium leprae</i> (+)	Sulphetrone or diphenylthiourea	
Myco tuberculosis (+)	Isoniazid plus amino-salicylic acid plus streptomycin	Special drugs for sensitized patients or resistant organisms
<i>Neisseria gonorrhoeae</i> (-)	Penicillin	Chloramphenicol, tetracyclines, erythromycin
<i>N. meningitidis</i>	Sulfonamides	Penicillin
<i>Pasteurella pestis</i> (-)	Streptomycin plus	Chloramphenicol plus
<i>Past. tularensis</i> (-)	tetracyclines	tetracyclines plus sulfonamides
<i>Proteus mirabilis</i> (-)	Penicillin	Neomycin
<i>P. vulgaris</i> (-)	Chloramphenicol	Neomycin
<i>Pseudomonas aeruginosa</i> (-)	Polymyxin	Tetracyclines, chloramphenicol
<i>Rickettsia</i> (-)	Chloramphenicol	Tetracyclines
<i>Salmonella</i> (-)	Chloramphenicol	Tetracyclines
<i>S. typhosa</i> (-)	Chloramphenicol	Penicillin
<i>Shigella</i> (-)	Sulfonamides or tetracyclines	Chloramphenicol
<i>Spirillum minus</i> (-)	Penicillin	Tetracyclines
<i>Staphylococcus</i>	Penicillin, methicillin	Chloramphenicol plus erythromycin
<i>Streptococcus</i> (+)	Penicillin	Erythromycin
<i>Str. faecalis</i> (+)	Penicillin plus streptomycin	Ristocetin
<i>Treponema pallidum</i>	Penicillin	Erythromycin, chloramphenicol, tetracyclines
<i>T. pertense</i>	Penicillin	

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## Infectious Diseases: Spirochetal

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### SYPHILIS

Syphilis is an acute and chronic, contagious, venereal granulomatous infection due to *Treponema pallidum*, a spirochetal organism which can infect any tissue or organ of the body. Since almost any disease may be mimicked by syphilis in one of its 3 clinical stages, it is referred to as the "great imitator." Although infection usually occurs during intercourse (entry into the body is gained through minor skin or mucosal lesions), transfer of organisms by infected blood and plasma and passage from the mother to the fetus through the placenta (congenital syphilis) is possible. Extragenital infection (tongue, breast, finger) may also occur. The organism cannot survive outside of body tissues and fluids, and infection other than through direct personal contact or through blood products is rare.

Penicillin therapy has greatly reduced the incidence of syphilis, but the disease is still a major public health problem, especially in low socio-economic areas. At present the incidence is rising, especially among teenagers and homosexuals.

Syphilis is an infectious granuloma. Initial infections, except for grossly visible lesions, are usually associated with little or no tissue reaction, damage, or disability. Late syphilis is associated with vasculitis, necrosis, tissue destruction, scar formation, and permanent damage and disability.

The natural history of acquired syphilis is usually divided into 2 stages: early, meaning primary and secondary syphilis, including relapsing forms, and late, including CNS, cardiovascular, ocular, and benign cutaneous, visceral, and osseous forms. A symptom-free but insidiously destructive latent form may divide the two. Congenital syphilis is considered separately.

#### Laboratory Diagnosis.

A. Serologic Tests for Syphilis (STS)  
Nontreponemal antigen tests are commonly

employed to measure the antibody complex (reagin) to *T. pallidum* which appears in the serum of syphilitic patients. They are of 2 types: (1) flocculation (VDRL, Kline, Kahn, Mazzini) and (2) complement fixation (Kolmer, Wasserman). Quantitative expression of the reactivity of the serum, based upon titration of geometrically progressive dilutions of serum, may be very valuable in establishing the diagnosis and in evaluating the efficacy of treatment. The STS usually becomes positive 4-6 weeks after infection, or 1-3 weeks after the appearance of the primary lesion. The STS titer is usually high in secondary syphilis and tends to be lower or even negative in late forms of syphilis, although this is highly variable. In tabes, for example, the reaction may be negative in 25-50% of cases, whereas in late visceral syphilis very high STS titers may be obtained. A falling titer in treated early syphilis or a falling or stable titer in latent or late syphilis indicates satisfactory therapeutic progress. Serologic tests are not completely specific and must be closely correlated with the history, physical findings, and other laboratory tests. Biologic "false-positive" serologic reactions are encountered in a wide variety of disorders such as the collagen diseases, infectious mononucleosis, malaria, many febrile diseases, leprosy, and non-syphilitic spirochetal infections; some individuals may for no apparent reason have a positive STS. False-positive reactions are usually of low titer and transient, but this is subject to considerable variation.

B. Dark-field Examination. In early syphilis *T. pallidum* may be demonstrated by dark-field examination of the serum from lesions or of material aspirated from regional lymph nodes. The dark-field examination requires experience and care in the proper collection of specimens and identification of spirochetes. Repeated examinations may be necessary. The spirochete is usually not found in any of the late syphilitic lesions by this technic.

**C. Spinal Fluid Examination** The CSF findings in neurosyphilis usually consist of elevation of total protein ( $> 40$  mg /100 ml.), increase in the cell count, and a positive reagin test (STS). Biologic false-positive reagin tests rarely occur in the CSF. Improvement of the CSF findings is of great prognostic value. A positive CSF in the absence of CNS symptoms (asymptomatic neurosyphilis) indicates the need for active penicillin treatment. In a small percentage of cases of CNS syphilis the CSF may be negative.

**D. Treponemal Antigen Tests** These "specific" tests for syphilis are complex, fairly expensive to perform, not readily available and by no means infallible. Blood or CSF specimens collected in special containers must be sent to regional medical or public health centers. The Treponema pallidum immobilization (TPI) and other newer tests utilizing the treponema antigen should be reserved for the following circumstances: (1) Diagnostic problem patients with no historical or clinical evidence of syphilis in which STS repeated serially at monthly intervals for 3 months are positive, conflicting, or equivocal. (2) Pregnant women with positive STS with no historical or clinical evidence of syphilis who are not currently under penicillin treatment. (3) Patients with clinical manifestations suggestive of late syphilis but who have negative, conflicting, or equivocal STS.

The treponemal antigen tests are of no value in early syphilis or in evaluating response to treatment. Test results are invalid if reported as "anticomplementary" or "unatisfactory."

## Prevention

Prophylactic advice should be given but avoidance of illicit sexual contact is the surest of all prophylactic methods.

**A. Mechanical** The standard rubber condom is effective but protects covered parts only. The exposed parts should be washed with soap and water as soon after contact as possible. This applies to both sexes.

**B. Antibiotic.** If there is a known exposure to infectious syphilis, abortive penicillin therapy may be used. Give 1.2 million units of repository penicillin I. M. in one dose.

## Treatment.

**A. Specific Measures** Carefully evaluate the physical status of the patient before beginning specific therapy.

**1. Penicillin**, as benzathine penicillin G, or procaine penicillin G with 2% aluminum monostearate (PAM), is the drug of choice for all forms of syphilis and other spirochetal infections. It is highly effective in early infections and variably effective in the late stages of syphilis. The recommended treatment schedules are included in the discussion of the various forms of syphilis.

**2. Other antibiotic therapy** - Oral tetracycline compounds and erythromycin are effective in the treatment of syphilis but are not recommended unless patients are sensitive to penicillin or have relapses following one or more courses of penicillin. Tetracycline, 30-40 Gm., or erythromycin, 20-30 Gm., are given over a period of 10-15 days. Since experience with these antibiotics in the treatment of syphilis is limited, careful follow-up is necessary.

**B. Local Measures (Mucocutaneous Lesions)** Local treatment is usually not necessary. No local antiseptics or other chemicals should be applied to a suspected syphilitic lesion until repeated dark-field examinations have been made. If, after the diagnosis has been established, the lesion should become secondarily infected, it may be treated as for any pyogenic ulceration. (This in addition to systemic antisyphilitic treatment.)

**C. Public Health Measures** Uncooperative and sexually promiscuous patients with infectious syphilis should be somehow isolated or quarantined until rendered noninfectious by preliminary therapy. Report all cases of syphilis to the appropriate public health agency.

## Complications of Specific Therapy.

The Jarisch-Herxheimer reaction is ascribed to the massive destruction of spirochetes by specific treatment and is manifested by fever and aggravation of the existing clinical picture and of the lesion itself. It is most likely to occur in early syphilis. Treatment is not discontinued unless the symptoms become severe or threaten to be fatal or in the presence of syphilitic laryngitis, auditory neuritis, or labyrinthitis, where such a reaction may cause irreversible damage. This reaction may be prevented or modified by simultaneous administration of corticosteroids. The reaction usually begins within the first 24 hours and usually subsides spontaneously within the next 24 hours without any treatment.

## Course & Prognosis.

Primary and secondary syphilis are self-limiting infections which resolve with little to



no residua. Late syphilis may be highly destructive and permanently disabling, and may lead to death. With treatment the STS will usually return to negative in early syphilis (primary and secondary). In late latent and late syphilis, serofalsiness is not uncommon, even after adequate treatment. In broad terms, if no treatment is given, about one-third of people infected with syphilis will undergo spontaneous cure, about one-third will remain in the latent phase throughout life, and about one-third will develop late lesions.

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## STAGES & TYPES OF SYPHILIS

### 1. PRIMARY SYPHILIS

This is the stage of invasion and may pass unrecognized. A history of contact with an infected individual 1-8 weeks previously may be obtained. The typical lesion is the chancre at the site or sites of inoculation, most frequently located on the penis, labia, or cervix. The chancre starts as a small erosion 10-80 days (average, 3-4 weeks) after inoculation which rapidly develops into a painless superficial ulcer with enlargement of regional lymph nodes, which are rubbery, discrete, and nontender. Secondary infection of the ulcer is not uncommon and may lead to pain. Healing occurs without treatment, but a scar may form, especially with secondary infection. The typical hunterian chancre is a firm eroded plaque 1-3 cm. in diameter.

The blood STS is usually positive 1-2 weeks after the primary lesion is noted, rising quantitative titers are especially significant since a positive STS may otherwise represent previous infection. The chancre will show organisms in over 95% of cases on repeated dark-field examination. The spinal fluid is normal at this stage.

The syphilitic chancre may be confused with chancroid, tularemia, or neoplasm. Any lesion on the genitalia should be considered as a possible primary syphilitic lesion.

### Treatment.

Give procaine penicillin with aluminum monostearate in oil (PAM), 600,000 units I.M. daily for 8 days, or benzathine penicillin G (Bicillin®), 1.2 million units in each buttock for total dose of 2.4 million units.

### 2. SECONDARY SYPHILIS

The secondary stage of syphilis is the period of dissemination, 7-10 weeks after exposure (2-3 weeks after appearance of the chancre). Systemic involvement with fever and generalized lymphadenopathy is often manifest. Almost any tissue of the body may be temporarily invaded and affected, but the most common manifestations are skin and mucosal lesions. The skin lesions are nonpruritic macular, papular, pustular, or follicular (or combinations of any of these types), although the maculopapular rash is the most common. The skin lesions usually are generalized, involvement of the palms and soles may be especially suspicious, since these areas are less commonly involved in other types of rashes. Annular lesions simulating ringworm are observed in Negroes. Mucous membrane lesions range from ulcers and papules of the lips, mouth, throat, genitalia and anus ("mucous patches") to a diffuse redness of the pharynx. Both skin and mucous membrane lesions are highly infectious at this stage. Specific lesions, condylomata lata, are fused papules on the moist areas of the skin and mucous membranes.

Meningeal, hepatic, renal, bone, and joint invasion and inflammation with resulting cranial nerve palsies, jaundice, nephrotic syndrome, and periostitis may occur. Alopecia (moth-eaten appearance), iritis, and iridocyclitis may also occur. A transient myocarditis manifested by temporary ECG changes has been noted.

Blood STS is positive in almost all cases. The cutaneous and mucous membrane lesions may show Treponema pallidum on dark-field examination. There is usually a transient CSF involvement, with pleocytosis and elevated protein, although only 5% of cases have positive CSF serologic reactions. A transient proteinuria with waxy casts is seen in mild renal involvement. Blood and urine tests may be positive for bile in hepatic involvement. Subperiosteal osteoporosis may be observed (rarely) on x-ray examination in cases of bone involvement.

The skin lesions may be confused with the infectious exanthems, pityriasis rosea, and drug eruptions. The visceral lesions may sug-

gest nephritis or hepatitis due to other causes. The diffusely red throat may mimic other forms of pharyngitis.

Treatment is as for primary adult syphilis.

### 3. RELAPSING SYPHILIS

After inadequate or inappropriate therapy secondary syphilis may relapse (often between the third and ninth post-treatment months). These relapses may be only serologic, with no clinical manifestations, or clinical, with recurrence (or first appearance) of any of the findings noted under secondary syphilis, above skin and mucous membrane, neurologic, ocular, bone, or visceral (although visceral relapse involving the liver has not yet been reported following penicillin therapy). Unlike the usual asymptomatic neurologic involvement of secondary syphilis, neurologic relapses may be fulminating, leading to death. It is important, however, to distinguish serologic relapse from the STS change from negative to positive that occurs despite penicillin therapy because of serologic lag, or that which occurs with intercurrent infections (biologic false-positive).

Treatment is as for primary adult syphilis.

### 4. LATENT ("HIDDEN") SYPHILIS

Latent syphilis is the clinically quiescent phase during the interval between disappearance of secondary lesions and before the appearance of tertiary symptoms. There are no clinical manifestations, and the only significant laboratory finding is a positive blood STS. To diagnose latent syphilis the CSF must be entirely negative, x-ray and physical examination must show no evidence of cardiovascular involvement, and false-positive tests for syphilis must be ruled out. The latent phase may last from months to a lifetime. Since the individual is potentially infectious only during the first 2-4 years of latent syphilis, this phase is divided into potentially infectious early latent (first 4 years) and noninfectious late latent (after 4 years).

It is important to differentiate latent syphilis from false-positive blood tests due to clerical errors, acute levers, yaws, infectious mononucleosis, malaria, leprosy, leishmaniasis, smallpox vaccination, lymphogranuloma venereum, systemic lupus erythematosus and other collagen diseases, and biologic false-positive reactions.

Treatment is as for primary syphilis.

Only a small percentage of blood STS will be

appreciably altered by treatment with penicillin. The treatment of this stage of the disease is intended to prevent the late sequelae.

### 5. LATE (TERTIARY) SYPHILIS

This stage may occur at any time after secondary syphilis, even after years of latency. Late lesions probably represent an allergic reaction of the tissue to the organism and are usually divided into 2 types: (1) A gummatous reaction with a relatively sudden onset, and (2) diffuse inflammation of a more insidious onset which characteristically involves the CNS and large arteries. Nodular, nodulo-ulcerative or gummatous lesions may appear on the skin, gummas may involve any area of the body, there may be evidence of aortic aneurysm, aortic insufficiency, or aortitis, or diffuse or localized CNS involvement may occur.

Late syphilis must be differentiated from neoplasms of the skin, liver, lung, stomach, or brain, other forms of meningitis, and primary neurologic lesions.

Repository penicillin (PAM), 600,000 units I. M. daily for a total of 12 million units, is recommended for the treatment of all forms of late syphilis. Reversal of positive STS does not usually occur. A second course of penicillin therapy may be given if necessary.

### COMMON TYPES OF LATE SYPHILIS

Although almost any tissue and organ may be involved in late syphilis, the following are the most common types of involvement.

#### Skin.

Cutaneous lesions of syphilis are of 2 varieties.

**A. Nodular or Nodulo-ulcerative Lesions** Multiple, flat, circumscribed, indurated, copper-colored lesions varying from 0.5-3 cm (1/4-1 1/4 inches) in diameter and covered with scales (syphiloderms). These lesions eventually ulcerate (nodulo-ulcerative) or resolve by forming atrophic, pigmented scars.

**B. Solitary Gummas** These start as painless, freely movable subcutaneous nodules which enlarge, attach to the overlying skin, eventually ulcerate, and present a gummy ulcerated base. Healing is by scarring which

often produces extensive disfiguring and disfiguring lesions of the face, scalp, forehead, and extremities.

#### Mucous Membranes.

Late lesions of the mucous membranes are nodular gumma or leukoplakia, highly destructive to the involved tissue

#### Skeletal.

Bone lesions are destructive, causing periostitis, osteitis, and arthritis with little to no associated redness or swelling but often marked myalgia and myositis of the neighboring muscles. The pain is especially severe at night.

#### Eyes.

Late ocular lesions are gummatous iritis, chorioretinitis, optic atrophy, and cranial nerve palsies, in addition to the lesions of CNS syphilis.

#### Respiratory System.

Respiratory involvement by late syphilis is caused by gummatous infiltrates into the larynx, trachea, and pulmonary parenchyma, producing discrete pulmonary infiltrates. There may be hoarseness, respiratory distress, and wheezing secondary to the gummatous lesion itself or to subsequent stenosis occurring with healing.

#### Gastrointestinal.

Gummas involving the liver produce the usually benign, asymptomatic *hepar lobatum*. Infiltration into the stomach wall causes a "leather bottle" stomach with epigastric distress, inability to eat large meals, regurgitation, belching, and weight loss. Occasionally a picture not unlike Laennec's cirrhosis is produced by liver involvement.

Of greatest importance, however, are the late lesions involving the cardiovascular and central nervous systems, since these are often progressive, disabling, and life-threatening. Cardiovascular and CNS involvement represent 10% and 20%, respectively, of all late lesions. Cardiovascular lesions not infrequently accompany CNS lesions.

#### Cardiovascular.

Cardiovascular lesions (about 10% of late syphilitic lesions) are often progressive, disabling, and life-threatening. CNS lesions are often present also. Involvement usually starts as an arteritis in the supracardiac portion of the aorta and progresses to cause one or more of the following: (1) Narrowing of the coronary ostia with resulting decreased coronary circula-

tion, angina, cardiac insufficiency, and acute myocardial infarction. (2) Scarring of the aortic valves, producing aortic insufficiency with its water-hammer pulse, aortic diastolic murmur, frequently aortic systolic murmur, cardiac hypertrophy, and eventually cardiac insufficiency. (3) Weakness of the aorta wall, with saccular aneurysm formation and associated pressure symptoms of dysphagia, hoarseness, brassy cough, back pain (vertebral erosion), and, not too infrequently, rupture of the aneurysm either into one of the bronchi or externally. Repeated attacks of respiratory infection are common as a result of pressure on the trachea and bronchi.

#### Neurosyphilis.

Neurosyphilis (20% of late syphilitic lesions, often present with cardiovascular syphilis) is, like cardiovascular syphilis, a progressive, disabling, and life-threatening complication. There are 4 clinical types:

(1) *Asymptomatic neurosyphilis*: This form is characterized by spinal fluid abnormalities (positive CSF, STS, increased cell count, occasionally increased protein) without symptoms or signs of neurologic involvement.

(2) *Meningovascular aphasia*: This form is characterized by meningeal involvement or changes in the vascular structures of the brain (or both), producing symptoms of low-grade meningitis (headache, irritability), cranial nerve palsies (basilar meningitis), unequal reflexes, irregular pupils with poor light and accommodation reflexes, and, when large vessels are involved, cerebrovascular accidents. The symptoms of acute meningitis are rare in late syphilis.

(3) *Tabes dorsalis*: This type of neurosyphilis is a chronic progressive degeneration of the parenchyma of the posterior columns of the spinal cord and of the posterior sensory ganglia and nerve roots. The symptoms and signs are those of impairment of proprioception and vibration, Argyll Robertson pupils (which react poorly to light but well to accommodation), and muscular hypotonia and hyporeflexia. Impairment of proprioception results in a wide-based gait and inability to walk in the dark. Paresthesias vary from analgesia (e.g., absence of pain sensation on squeezing the testicles) to the sharp recurrent pains in the muscles of the leg, described as "shooting" from the skin to the bone (shooting or lightning pains). Crises are also common in tabes: gastric crises, consisting of sharp abdominal pains with nausea and vomiting (simulating an acute abdomen), laryngeal crises, with paroxysmal cough and dyspnea; urethral crises, with painful bladder spasms, and rectal and anal crises.

Crises may begin suddenly, last for hours to days and cease abruptly. Neurogenic bladder with overflow incontinence is also seen. Trophic, painless ulcers may occur over pressure points on the feet. Joint damage may occur as a result of lack of sensory innervation (Charcot joint).

(4) Paresis This is a generalized involvement of the cerebral cortex. The onset of clinical manifestations is insidious. There is usually a decrease in concentrating power, memory loss, dysarthria, tremor of the fingers and lips, irritability, and mild headaches. Most striking is the change of personality, the patient becomes slovenly, irresponsible, confused, and psychotic. Combinations of the various forms of neurosyphilis (especially tabes and paresis) are not uncommon.

Special considerations in treatment of neurosyphilis. The most important consideration is to prevent neurosyphilis by early diagnosis and adequate treatment and follow-up of early syphilis. Examination of all syphilitic patients for evidence of nervous system involvement must be a regular part of the follow-up examination. The pre-treatment clinical and laboratory evaluation should include detailed neurologic, ocular, and psychiatric examinations and a CSF examination. The high rate of coexistence of cardiovascular and CNS syphilis should be considered.

Give repository penicillin, 600,000 units I. M. daily to a total of 12 million units.

All patients must have a spinal fluid examination 3 months following completion of anti-syphilis therapy. The adequacy of response is at times difficult to evaluate (especially during a short period of observation), but it may be gauged by clinical improvement and effective and persistent reversal of CSF changes. A second course of penicillin therapy may be given if necessary.

## 6 PRENATAL SYPHILIS

Expectant mothers who have syphilis must be convinced of the urgent necessity for therapy. It is the physician's responsibility to make certain that appropriate treatment is carried out immediately. Penicillin dosage schedules as advised for primary and secondary syphilis are satisfactory. When therapy is instituted after the seventh month in women with untreated early syphilis, larger doses of penicillin are advised.

Penicillin is curative in more than 90% of cases even when syphilis is discovered in the last trimester of pregnancy.

Follow-up must consist of monthly physical examinations and quantitative blood STS until delivery and for a month after delivery. If there is any clinical evidence of relapse, a failure of fall of blood STS titer, or a rise of STS titer, treatment should be repeated. The STS cannot always be converted to negative in mothers with late latent syphilis. In case of previously untreated or inadequately treated early latent syphilis, if the original STS titer does not significantly decline within 3 months after treatment, retreatment is advisable.

The infant should be examined for the stigmata of syphilis at birth and again at intervals of 2 or 3 weeks for 4-6 months. If the maternal blood is positive, a positive cord blood STS is of no diagnostic value. However, if the infant's blood is followed serially by quantitative blood STS at two-week intervals for 4 months, a sustained or rising STS titer would indicate a diagnosis of congenital syphilis and a need for treatment.

## 7 CONGENITAL SYPHILIS

The clinical manifestations of congenital syphilis are quite similar to those of the acquired form except for the rather indefinite clinical course and the absence of primary lesions. There is usually a family history of syphilis. Skin and mucous membrane lesions are present at birth or in early infancy. Characteristic stigmata of congenital syphilis include interstitial keratitis, Hutchinson's teeth, eighth nerve deafness (Hutchinson's triad), saddle nose, rhagades, saber shins and other bone changes, and mental retardation. The STS is usually strongly positive at birth but gradually becomes negative over a period of years. Any of the tertiary sequelae of the adult disease (CNS, visceral, or cardiovascular) may occur.

Early congenital syphilis (< 2 years of age) is treated with 50,000 units of benzathine penicillin G/Kg as a single injection, or 50,000 units PAM/Kg I. M., repeated in 2-3 days. The treatment of late congenital syphilis is as for late latent syphilis. Neurosyphilis of congenital origin should be treated as the acquired form.

## OTHER TREPONEMATOSES\*

ENDEMIC SYPHILIS  
(Bejel, Skerljevo, etc.)

Endemic syphilis is an acute and chronic infection caused by an organism morphologically indistinguishable from *Treponema pallidum*, it is distinguished from sporadic syphilis by its occurrence in children of crowded, poor households in particular localities, by virtual absence of primary lesions, and the predilection of secondary lesions for oral and nasopharyngeal mucosa as well (in places) as the soles (plantar hyperkeratosis). It is distinguished from yaws by its occurrence in areas in which yaws is not endemic and by the absence of primary lesions and the presence of buccal lesions. It may be confused with angular stomatitis due to vitamin deficiency. It has been reported in a number of countries including Latin America, often with local names: bejel in Syria and Iraq, skerljevo in Bosnia, dichuchwa, njovera, and sita in Africa. Each has local distinctive characters.

Secondary oral lesions are the most common manifestations. Generalized lymphadenopathy and secondary and tertiary bone lesions are common in bejel. Secondary lesions tend to heal in about a year.

Laboratory findings and treatment are the same as for primary syphilis.

## PINTA

Pinta is a nonvenereal spirochetal infection caused by *Treponema carateum*. It occurs endemically in rural areas of Latin America, especially in Mexico, Colombia, and Cuba, the Philippines, and some areas of the Pacific. A nonulcerative, erythematous primary papule spreads slowly into a papulosquamous plaque showing a variety of color changes (slate, lilac, black). Secondary lesions resemble the primary one and appear within a year after it. These appear successively, new lesions together with older ones, and are commonest on the extremities but may cover most of the body. Mild local lymphadenopathy is common. There

is later atrophy and depigmentation. Some cases show pigment changes and atrophic patches on the soles and palms, with or without hyperkeratosis, which are indistinguishable from "crab yaws."

Diagnosis and treatment are the same as for primary syphilis.

YAWS  
(Frambesis)

Yaws is a contagious disease largely limited to tropical regions which is produced by *Treponema pertenue*. It is characterized by granulomatous lesions of the skin, mucous membranes, and bone. Yaws is rarely fatal, although if untreated it may lead to chronic disability and disfigurement. Yaws is acquired by direct nonvenereal contact. The disease is usually acquired in childhood, although it may occur at any age. The "mother yaw," a painless papule which later ulcerates, appears 3-4 weeks after exposure. There is usually associated regional lymphadenopathy. Six to 12 weeks later, similar secondary lesions appear and last for several months or years. Late gummatous lesions may follow, with associated tissue destruction and alteration involving large areas of skin and subcutaneous tissues. The late effects of yaws, with bone change, shortening of digits, and contractions, may be confused with similar changes occurring in leprosy. CNS, cardiac, or other visceral involvement is rare. The Wassermann and flocculation tests are positive, and the spirochetes may be demonstrated by dark-field examination.

Cleanliness of lesions is most important in treatment. Specific measures consist of giving one of the following (1) penicillin procaine, 300,000 units I. M. daily for 7-10 days, (2) one of the tetracyclines, 0.5 Gm. every 6 hours for 10 days, or (3) dichlorophenarsine (Cloarsen®), 40 mg. I. V. weekly for 3-6 weeks.

\*Turner, L. H.: Notes on the treponematoses with an illustrated account of yaws. Bull. No. 9 Inst. Med. Res. Malaya, 1959.

## MISCELLANEOUS SPIROCHETAL DISEASES

### RELAPSING FEVER

Relapsing fever is the name of a group of clinically similar acute infectious diseases caused by several different species of spirochetes of the genus *Borrelia*. The disease is transmitted to man by insect vectors (head and body lice and ticks). The insect is infected by feeding on human acute cases (lice) or the animal reservoir (ticks) and transmits the disease to humans when insect feces or crushed insects are rubbed into the bite puncture wound, excoriated areas of skin or the eyes. The disease is endemic in various parts of the world including western United States. The incubation period is 2-15 days (average about 7 days).

#### Clinical Findings

**A. Symptoms and Signs.** The disease is characterized by relapses occurring at intervals of 1-2 weeks after the preceding episode with an interim asymptomatic period. The relapses duplicate the initial attack but become progressively less severe. Recovery occurs after 2-10 relapses.

The attack is of sudden onset with fever, chills, tachycardia, nausea and vomiting, myalgia, arthralgia, bronchitis, and a dry non-productive cough. Hepatomegaly and splenomegaly appear later. Jaundice may be present. An erythematous rash appears early in the course of the disease over the trunk and extremities, followed later by rose-colored spots in the same area. Petechiae may also be present. In severe cases neurologic and psychic manifestations are present. After 3-10 days the fever falls by crisis. Jaundice, iritis, conjunctivitis, cranial nerve lesions, and uterine hemorrhage are more common in the relapse.

**B. Laboratory Findings.** During the acute episodes the urine shows protein, casts, and occasionally erythrocytes. The blood shows a marked polymorphonuclear leukocytosis and in about one-fourth of cases a false positive STS. During the paroxysm spirochetes may be found in the patient's blood on dark-field examination of a blood smear stained with Wright's or Giemsa's stain, or the blood may be injected into a rat and the spirochetes found 3-5 days later in the tail blood. The Weil-Felix test may be positive in a titer of 1:80 or more.

#### Differential Diagnosis

The early symptoms of relapsing fever may be confused with many other acute infections; however, as the disease progresses, its nature usually becomes evident. Later manifestations of relapsing fever are occasionally confused with those of malaria (relapses), leptospirosis (spirochetes, jaundice), dengue (severe myalgia), yellow fever (jaundice), and typhus (skin lesions).

#### Treatment

Treat either with (1) aqueous penicillin 50,000 units I.M. every 3 hours or penicillin G procaine 300,000 units I.M. daily for 10 days or (2) tetracycline drugs 0.5 Gm. every 6 hours orally. Chloramphenicol (Chloromycetin®) or oxytetracycline (Terramycin®) is often of value.

#### Prognosis

The overall mortality rate is usually about 5%. Fatalities are most common in the old debilitated or very young patients. With treatment the initial attack is shortened and relapses largely prevented.

Hirschboeck M.M. The use of chloramphenicol in relapsing fever. *Am J Trop Med* 3: 712-3, 1954.

Varma M.G. Infections of *Ornithodoros* ticks with relapsing fever spirochetes and the mechanism of their transmission. *Ann Trop Med* 50: 18-31, 1956.

### RAT BITE FEVER

(Spirillary Rat bite Fever, Sodoku)

Rat bite fever is an acute infectious disease caused by the *Spirillum minus* and transmitted to man by the bite of a rat. The organism gains entry into the rat's oral cavity from the drainage of a primary eye infection. The incubation period is 5-28 days.

#### Clinical Findings

**A. Symptoms and Signs.** The original rat bite, unless infected, heals promptly, only to be followed after the incubation period by a flare-up of the original site. The area of the rat bite then becomes swollen, indurated, and painful, assumes a dusky purplish hue, and may ulcerate. Regional lymphangitis and lymphadenitis, fever, chills, malaise, myalgia, arthralgia, and headache are present. Splenomegaly may occur. A dusky red, sparse maculopapular rash appears on the trunk and extremities.

After a few days both the local and systemic symptoms subside, only to reappear again in a few days. This relapsing pattern of fever of 24-48 hours alternating with an equal afebrile period becomes established and may persist for weeks. The local and systemic findings, however (including the rash), usually recur only during the first few relapses.

**B. Laboratory Findings:** Leukocytosis is often present, and a blood STS may be falsely positive. The organism may be identified in dark-field examination of the ulcer exudate or aspirated lymph node material or by animal inoculation of exudate or blood. The organism cannot be cultured in artificial media.

#### Differential Diagnosis.

Rat-bite fever must be distinguished from the rat-bite-induced episodic fever, lymphadenitis, and rash of streptobacillary fever. In the latter the presence of septic nonmigratory polyarthritides, a specific agglutination titer, and the isolation of the causative organism differentiates the disorder from spirillary rat-bite fever. Rat-bite fever may also be distinguished from tularemia and relapsing fever by identification of the causative organism.

#### Treatment.

Treat with penicillin, 100,000 units every 3 hours I. M.; penicillin procaine G, 300,000 units I. M. every 12 hours, or tetracycline drugs, 0.5 Gm. every 6 hours. Give supportive and symptomatic measures as indicated.

#### Prognosis.

The reported mortality rate is about 10%, but this should be markedly reduced by prompt diagnosis and treatment.

Adams, J. M., & C. M. Carpenter. Rat-bite fevers. *P. Clin. North America* 2:101-8, 1955.

## LEPTOSPIROSIS (Including Weil's Disease)

#### Essentials of Diagnosis.

- Sudden onset of fever, chills, headache, muscle pains and tenderness, photophobia, and conjunctival redness.
- Hepatitis, nephritis, meningitis, pneumonitis, iridocyclitis and skin rash may occur.
- Proteinuria, leukocytosis.
- Organism identified by smear, animal inoculation, culture, and rising agglutination titer.

The diagnosis is frequently missed in the absence of jaundice and erroneously diagnosed as dengue or appendicitis. Leptospirosis with jaundice must be distinguished from hepatitis, yellow fever, and relapsing fever. Leptospirosis may present as grippé, aseptic meningitis, or pretibial fever.

#### General Considerations.

Leptospirosis is an acute infection caused by any of several *Leptospira* species. The 3 most common species and their reservoirs of infection are *Lept. icterohaemorrhagiae* of rats, *Lept. canicola* of dogs, and *Lept. pomona* of cattle and swine. Several other species, some as yet unidentified serologically, can also cause the disease, but *Lept. icterohaemorrhagiae* causes the most severe illness. The disease is world-wide in distribution, and the incidence is nearly always higher than usually supposed. The parasite, which is non-pathogenic for its animal reservoir, is transmitted to man by the ingestion of food and drink contaminated by the urine of the reservoir animal. The organism may also enter through minor skin lesions and probably the conjunctivas also, and many infections have followed bathing in contaminated pools or streams. The disease is an occupational hazard among sewer workers, rice-planters, and farmers. The incubation period is 5-13 days.

#### Clinical Findings.

**A. Symptoms and Signs:** There is a sudden onset of fever to 38.9-40°C. (102-104°F.), chills, abdominal pains, vomiting, and myalgia especially of the calf muscles. Extremely severe headache is usually present. The conjunctivas are markedly reddened. The liver may be palpable, and in about 50% of cases (most commonly in *Lept. icterohaemorrhagiae* infections) jaundice is present on about the

fifth day and may be associated with nephritis. Splenomegaly is uncommon except in pretibial fever. Capillary hemorrhages and purpuric skin lesions may also appear. Meningeal irritation and associated findings may occur. In pretibial fever patchy erythema occurs on the skin of the lower leg and may be generalized.

**B Laboratory Findings** The leukocyte count may be normal or as high as 50 000/cu mm with neutrophils predominating. The urine may contain bile protein casts and red cells. Oliguria is not uncommon and in severe cases uremia may occur. In cases with meningeal involvement organisms may be found in the CSF. The organism may be identified by dark field examination of the patient's blood (during the first 10 days) by guinea pig inoculation or by culture on Korthof's medium. The organism may also be isolated from the urine from the tenth day to the sixth week. Specific agglutination titers develop after 7 days and may persist at high levels for many years.

### Complications

Myocarditis renal failure and massive hemorrhage are not common but are the usual cause of death.

### Treatment

Treat as early as possible (and continue treatment for 5 days) with tetracyclines 0.5 Gm every 6 hours or penicillin 600 000 units I M every 3 hours for one day and then every 6 hours. Observe for evidence of renal failure and treat as necessary.

### Prognosis

Without jaundice the disease is almost never fatal. With jaundice the mortality rate is about 15%. Death occurs from extreme toxemia or one of the above complications.

Edwards G A. Clinical characteristics of leptospirosis. Observations based on a study of twelve sporadic cases. *Am J Med* 27:4 17 1959.

Edwards G A & B M Domm. Human leptospirosis. *Medicine* 39:117 56 1960.

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## Infectious Diseases: Protozoal

J. Ralph Audy & Frederick L. Dunn

### ✓ AMEBIASIS

#### ✓ Essentials of Diagnosis

- Recurrent bouts of diarrhea, stool semi-fluid, without pus and with only flecks of blood
- With acute attack, low-grade fever, nausea, vomiting, malaise, right lower quadrant cramps.
- Between acute attacks, intermittent loose bowel movements and abdominal cramps.
- Occasionally hepatitis or liver abscess (without dysentery)
- Organisms demonstrated in the stool or aspirate (abscess material)

Under sanitary conditions in temperate zones, amebic diarrhea (dysentery) must be distinguished from ulcerative colitis (by sigmoidoscopy and stool examinations) and acute nonspecific colitis (by stool examinations), in tropical areas or under insanitary conditions, it must be distinguished from bacillary dysentery, in which there is a more acute onset, with tenesmus, and frequent, watery, purulent, bloody stools. At times amebic dysentery must be distinguished also from schistosomiasis, balantidiasis, regional enteritis, and tuberculous enterocolitis. These may be distinguished by the sigmoidoscopic and barium enema findings, and the identification of a specific organism. Ameboma is occasionally confused with colon carcinoma. Amebic hepatitis and abscesses must be differentiated from other forms of hepatitis and abscesses, especially bacterial abscess. A positive complement fixation test in amebic abscess aids greatly in this differentiation, but this test is not customary in the United States.

#### General Considerations.

Amebiasis is an infectious disease caused by the protozoan, *Entamoeba histolytica*. It is cosmopolitan in distribution, may occur in epidemics in temperate climates, and is a risk to newcomers in the tropics. Amebiasis is divided into (1) intestinal amebiasis, which includes both acute and chronic amebic dysentery and the asymptomatic carrier state, and (2) extra-intestinal amebiasis, which is mostly confined to the liver.

The organism exists in 2 forms (1) a motile ameba or trophozoite which occurs in the intestinal tissue and liver, and in the lumen and stools during dysenteric attack, and (2) a cyst which occurs only in the intestinal lumen and stool. The cyst may remain viable for several weeks at room temperature. Both trophozoites and cysts must be distinguished from those of other nonpathogenic amebas occurring in man.

The organism gains entry into man in food and drink containing cysts from feces. The cyst passes into the intestine and excysts in the region of the ileocecal valve. The resulting motile trophozoite with its proteolytic enzymes penetrates into the mucosa of the colon, the greatest density of organisms is at the site of the greatest fecal stasis, i.e., the cecum, descending colon, sigmoid colon, and rectum. The site of penetration of the trophozoite first becomes a micro-abscess, which soon enlarges and ulcerates to produce a shallow, undermined ulcer with a ragged edge. The ulcer may remain discrete or may coalesce with others to cause extensive bowel involvement. Occasionally the bowel may perforate.

There is evidence that the amebas become particularly invasive in the presence of mild bacillary infection, either because of mucosal damage or because of some synergistic action, or both. There is also evidence that the diet (but not particularly the nutritional state) is important in determining amebic pathogenicity.

During invasion of the mucosa, emboli which may contain trophozoites are carried to

the liver through the portal system. These trophozoites are usually destroyed, but a diffuse hepatitis may develop. Trophozoites may occasionally remain active and multiply, producing an amebic abscess by extension or by fusion of multiple foci. This may follow a subclinical intestinal infection. The incidence of liver abscess is not related to the severity of preceding amebic dysentery, and only about one-third of cases with liver involvement give a history of amebic dysentery.

Asymptomatic infection (cyst-passers, carrier state) is common. Up to 10% of people in the United States carry the infection, with a maximum incidence in the southern states, and 50% or more in highly endemic areas where there is no sanitation and where human feces are used as fertilizer. Cyst-passers may be convalescents or may have no known relevant history.

### Clinical Findings

**A Symptoms and Signs.** The onset is seldom abrupt. Increasingly severe diarrhea develops over several days and is associated with weakness, nausea, vomiting, cramping pain in the right lower quadrant, and prostration. Acute onset often signifies a concurrent *Shigella* infection or dietary indiscretion. The stools (5-10 a day) are brown, semifluid, and foul-smelling, with flecks of mucus and blood. Fever is absent to low-grade. Urticaria may occur. The acute attack usually subsides spontaneously, and the individual has residual complaints of abdominal cramps, loose bowel movements (especially after meals), weakness, and malaise. Acute symptoms usually recur at variable intervals, and are often precipitated by alcoholic excess, emotional stress, or fatigue. Without treatment there is progressive emaciation and anemia.

**Liver involvement** evokes the usual symptoms of hepatitis, including fever and is best detected by tenderness and possibly enlargement on palpation and firm persussion. About one-fourth of cases show signs of hepatitis which are often not due to trophozoite activity. The manifestations of hepatitis due to trophozoites should subside about a week after treatment is started. If an abscess is present the liver is usually enlarged. Onset is often insidious, and the patient may have undergone much investigation with many tentative diagnoses until he develops a painful friction rub over the abscess or signs of right lower chest involvement. The lungs and pleural cavities (almost always on the right side) may be involved secondarily from an abscess, or (rarely) there may be a pulmonary abscess.

**B Laboratory Findings.** In diarrhea or dysentery, the trophozoites and cysts may be identified in the stool or by examination of tissue obtained from the ulcers at the time of sigmoidoscopic examination. The trophozoites are not found in formed stools. They are large, progressively motile, and may contain ingested red cells (a most important feature). Trophozoites and cysts must be distinguished from those of the nonpathogenic amebas, *E. coli*, *Iodamoeba bütschlii*, *Dientamoeba fragilis*, and *Endolimax nana*. In the stool leukocytes and macrophages are relatively scarce, although Charcot-Leyden crystals may be present. The WBC is elevated during the acute attack and with hepatic involvement, there is, however, no eosinophilia. Anemia may be present in long-standing disease. In hepatic amebiasis, however, the stool is positive in only about one-third of cases.

With liver abscess, material for examination may be obtained by aspiration, although the central markedly necrotic material is usually free from organisms. The appearance is normally characteristic and has been described as resembling "anchovy paste." It is important to divide the aspirated material into a succession of 20-30 ml. samples as it is taken so that the last sample only may be examined. Do not send large samples to the laboratory.

A complement fixation test is often positive in cases of hepatic involvement.

Sigmoidoscopic examination may reveal the ulcerative lesions, with intact intervening mucosa. It is very valuable in experienced hands, and should be adopted as a routine.

### Complications.

Amebas from the intestine may rarely travel to and infect the lungs, brain, or skin. Perforation of the bowel may also occasionally take place, and an untreated hepatic abscess may perforate into the adjacent pleural space to produce an effusion and a pneumonitis. The bowel wall in amebic dysentery is very friable, and surgery is contraindicated in healing of the intestinal tissue. Extensive scarring may take place that can lead to intestinal obstruction, but healing may also often be complete and rapid. Amebomas may resolve completely with little residual fibrosis.

### Treatment.

Bed rest is recommended for all patients with frank symptoms and is imperative for any patient receiving emetine (see below). If diarrhea is present, dietary measures are indicated as for nonspecific diarrhea. In hepatic amebiasis give a diet as outlined for chronic hepatic disease. If anemia is present, iron

therapy (see p 264) should be given. A relatively high-protein diet is generally indicated.

#### A Intestinal Amebiasis, Acute or Chronic Amebic Dysentery

1 Specific drugs - These are of 3 distinct types, acting respectively against intestinal amebas, associated pathogenic intestinal bacteria, and extra-intestinal amebas. Some drugs act against both bacilli and amebas in the intestine, but no drug is equally effective against both. A rational approach to therapy is to attack the associated bacteria whenever they are suspected of being active and to treat for extra-intestinal infection only when indicated by follow-up. In some cases of chronic dysentery extra-intestinal invasion may be assumed for the sake of safety and a combination of amebicides given; this is rarely necessary in the U S, however.

The specific intestinal amebicides are (1) emetine and bismuth iodide (EBI<sup>®</sup>), (2) the arsenicals, carbarsone and glycoflarsol (Millibis<sup>®</sup>), and (3) iodochlorhydroxyquin (Vioform<sup>®</sup>). Emetine parenterally helps control severe amebic dysentery, but will not cure if given alone. The antibiotics paromomycin (Humatin<sup>®</sup>) (promising but still under trial) and fumagillin (Fumidil<sup>®</sup>) (now regarded with less favor than other measures) directly affect both bacilli and amebas, but tetracyclines control only the associated bacillary infection. Broad-spectrum antibiotics are preferable since a variety of bacteria appear to be associated with acute dysentery. Chloroquine and emetine are specific against extra-intestinal amebas.

The patient must be closely observed for toxic reactions, especially when taking carbarsone, glycoflarsol, or iodochlorhydroxyquin.

(1) Emetine and bismuth iodide (EBI<sup>®</sup>), enteric-coated, 0.2 Gm. (3 gr.) daily, may be given in 3 divided doses, preferably with sedation for the first few days to minimize nausea. This also controls extra-intestinal amebiasis to a considerable extent.

(2) Carbarsone, 0.25 Gm. (3 3/4 gr.) t i d orally for 7-10 days, or glycoflarsol (Millibis<sup>®</sup>) 0.5 Gm. t i d for 7 days. These arsenicals are contraindicated in hepatic disease. Inspect daily for toxic symptoms (fever, abdominal discomfort or pain, nausea and vomiting, diarrhea, dermatitis) and discontinue at once if toxic effects are suspected.

(3) Iodochlorhydroxyquin (Vioform<sup>®</sup>), 0.25 Gm. (3 3/4 gr.) t i d orally for 14 days. Contraindicated in renal and possibly hepatic disease, but toxic effects (indigestion, diarrhea) are uncommon.

(4) Oxytetracycline (Terramycin<sup>®</sup>), 25 mg

/Kg. daily for 10-14 days in divided doses every 6 hours. Used for acute amebic dysentery, combined with a direct-acting amebicide.

2 Evaluation of therapy - Every patient must be followed for about 2 weeks after treatment and the stools examined for 6 successive days - or better still, at intervals of a few days. If stools are positive, re-examine the patient completely, check carefully for possible reinfection in his home or at work and treat with a specific amebicide, possibly combined with erythromycin. If stools are negative, check by sigmoidoscopy and give no further treatment. Re-examine stools daily for 3-6 consecutive days after 3 months, and again after another 6 months or whenever symptoms appear. It is advisable to repeat sigmoidoscopy.

#### B Hepatic Amebiasis

1 Measures for hepatitis -

(1) Chloroquine phosphate (Araien<sup>®</sup>) is the drug of choice in hepatic amebiasis. Give 0.5 Gm. (or 3 Gm. of the base) b i d for 2 days, followed by 0.5 Gm. daily for 10 days.

(2) Emetine hydrochloride injection, 65 mg (1 gr.) daily i m or subcut for 6 days. Contraindicated in myocardial disease. Reserve for accurately diagnosed extra-intestinal amebiasis which has failed to respond to chloroquine. Confine the patient to bed and chart his pulse hourly and his BP twice a day, record ECG before and after therapy. Withdraw emetine on suspicion of toxicity, as manifested by nausea, vomiting, muscular weakness, neuritis, myocarditis, and prostration.

(3) Emetine and bismuth iodide (EBI<sup>®</sup>) given as above may be considered.

(4) General supportive measures should be instituted as for infectious hepatitis. A two-week rest period may be followed by a repeat course of treatment with chloroquine or emetine, with or without erythromycin as indicated.

(5) Follow all cases at intervals as for intestinal amebiasis with special attention to general health, appetite, gain in weight, and liver function.

2 Measures for liver abscess -

(1) Treat as for hepatitis, preferably combining chloroquine with emetine. If the patient responds, continue general measures and repeat the course of treatment after 1-2 weeks. It may be necessary to follow a course of chloroquine with a course of emetine and erythromycin and perhaps a later course of chloroquine. As with asymptomatic amebiasis, however, the tendency to overtreat must be avoided. Time must be allowed for resolution.

(2) Localize the abscess as accurately as possible (x-rays may help), and drain it by aspiration under strict aseptic conditions. Repeat aspiration if necessary. Open drainage must be avoided unless the abscess is secondarily infected, in which case proceed as described below. Repeat drug therapy.

(3) Secondarily infected abscess - Aspirated material contains pus and organisms. Identify the organisms by culture and determine antibiotic sensitivity. Treat with a full course of chloroquine combined with tetracycline or another indicated antibiotic. Consider open drainage and irrigations with antibiotic solution. Repeat the course after 1-2 weeks. Be on guard against involvement of the right chest and possible perforation through the diaphragm.

**C Amebiasis of Other Organs** Treat as for hepatic amebiasis.

**D Asymptomatic Amebiasis ("Carrier State")**

1 Iodochlorhydroxyquin (Vioform®), 0.25 Gm (33/4 gr) t.i.d. orally for 14 days, or carbarsone, 0.25 Gm (33/4 gr) t.i.d. orally for 7-10 days, or glycothiarsol (Milbilis®), 0.5 Gm, t.i.d. for 7 days, with or without oxytetracycline.

2 Avoid overtreatment, follow with repeated stool examinations (as for amebic dysentery), and investigate possible sources of reinfection after therapy.

3 The cyst-passer must be considered wholly within the context of his surroundings, his similarities to and differences from the population in contact, and the prevailing endemicity of amebic dysentery. Thus he may sometimes require continued surveillance and treatment or - for example, in most parts of the United States - he may at times be safely ignored. It is very important to avoid, if possible, the disturbing psychologic effects of awareness of passing cysts and being a potentially dangerous person.

4 Some clinicians recommend a course of chloroquine or emetine (as for hepatic amebiasis) as a precaution against the possibility of accompanying early extra-intestinal infection. Others prefer to withhold such therapy until clinical indications for it are clear. The latter course seems more rational. The passage of small cysts (from *E. hartmanni* or *E. histolytica hartmanni*) is commonly regarded as not requiring therapy.

**E. Follow-up Care:** A complete follow-up examination consists of sigmoidoscopy and study of 6 successive stools (at least one following a saline purge), daily or at intervals of

a few days. The examination should be repeated within one year and specific treatment given only if amebas are demonstrated. Consider the possibility of secondary infection. Irritation of bowel by chemotherapy or overtreatment, and psychoneurosis in all patients in whom symptoms persist or recur without demonstration of amebas. The manner in which follow-up is conducted must not lead the patient to believe that he is "not cured."

#### Prognosis.

Untreated, the mortality rate from amebic dysentery may reach 20-40%, with the highest incidence in the debilitated patient and in chronic recurrent cases. This incidence is reduced to 1-5% in treated cases. Amebiasis affecting the liver varies greatly in its mortality rate, depending upon the extent of the involvement, the number of abscesses, their accessibility to drainage, and the presence of secondary infections of the abscess.

Anderson, H. H., "Newer drugs in amebiasis," *J. Pharmacol. & Exper. Therap.* 1:78-86, 1960.

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Dooner, H., Saavsdra, J., & T. Labrin: Combined therapy in amebiasis. *Gastroenterology* 38:819-22, 1959.

Kean, B. H., Gilmore, H. R., & W. W. Van Stone: Fatal amebiasis: report of 148 cases from the Armed Forces Institute of Pathology. *Ann. Int. Med.* 44:831-34, 1956.

## MALARIA

#### Essentials of Diagnosis

- Paroxysms (often periodic) of chills, fever, and sweating.
- Splenomegaly, anemia, leukopenia.
- Delirium, coma, convulsions, gastrointestinal disorders, and jaundice.
- Characteristic parasites in erythrocytes, identified in thick or thin blood films.

Diagnosis is not difficult when classical periodic paroxysms occur, but the clinical appearance is often modified by the degree of immunity. Modified malaria must be distinguished from a variety of other diseases causing intermittent fevers. Infections may cause few or no symp-

toms in hyperendemic areas. The certain diagnosis of malaria depends upon the detection of the parasites, usually in the peripheral blood.

#### General Considerations

Four species of ameboid protozoan parasites of the genus *Plasmodium* are responsible for human malaria. Today the infection is generally limited to the tropics and subtropics, in years past malaria transmission occurred in many temperate regions. Temperate zone malaria is usually unstable and relatively easy to control or eradicate. Tropical malaria is often more stable. In the tropics malaria generally disappears at altitudes above 6000 feet. The most common parasites, *P. vivax* and *P. falciparum*, are found throughout the malaria belt. *P. malariae* is also broadly distributed but less common. The fourth parasite, *P. ovale*, is rare, but in West Africa it seems to replace *P. vivax*. The infection can be artificially transmitted by blood transfusion from an infected donor, but in nature infection takes place through the bite of an infected female *Anopheles* mosquito. The mosquito is the host during the sexual phase of the life cycle, man is the host for the asexual developmental stages. After an infective bite the first stage of development in man takes place in the liver. Parasites escape from the liver into the blood stream 5 1/2-11 days later. Erythrocytes are invaded the parasites multiply, and 48 hours later (or 72 in the case of *P. malariae*) the red cells rupture, releasing a new crop of parasites. This cycle of invasion, multiplication, and red cell rupture may be repeated many times. Symptoms do not appear until several of these erythrocytic cycles have been completed. The incubation period varies considerably depending upon the species and strain of parasite, the intensity of the infection, and the immune status of the host. For *P. vivax* and *P. falciparum* it is usually 10-15 days but it may be much longer (in some cases even months). The *P. malariae* incubation period averages about 28 days. *P. falciparum* multiplication is confined to the red cells after the first cycle in liver cells (the pre-erythrocytic stage). Thus any treatment which eliminates *falciparum* parasites from the blood stream will cure the infection. Without treatment the infection will terminate spontaneously in less than 2-3 years (usually 6-8 months). The other 3 species continue to multiply in liver cells long after the initial blood stream invasion. This exo-erythrocytic cycle of multiplication coexists with the erythrocytic cycle and may persist after parasites have apparently disappeared from the blood stream. Successful cure of

*P. vivax*, *P. ovale*, and *P. malariae* infections requires treatment aimed not only at parasites in red cells but also at those in the liver. *Vivax* and *ovale* infections may persist without treatment for as long as 5 years, *P. malariae* infections which lasted for 40 years have been recorded.

#### Clinical Findings

**A Symptoms and Signs** The paroxysms of malaria are closely related to events in the blood stream. The chill, lasting from 15 minutes to an hour, begins as a generation of parasites ruptures their host red cells and escapes into the blood. Nausea, vomiting, and headache are common at this time. The succeeding hot stage, lasting several hours, is accompanied by a spiking fever, sometimes reaching 40°C (104°F) or higher. During this stage the parasites presumably invade new red cells. The third or sweating stage concludes the episode. The fever subsides and the patient frequently falls asleep to wake feeling relatively well. In *vivax* (benign tertian malaria), *ovale* and *falciparum* (malignant tertian malaria) infections, red cells are ruptured and paroxysms occur every 48 hours. In *malariae* infections (quartan malaria) the cycle takes 72 hours. In the early stages of infection the cycles are frequently asynchronous and the fever patterns irregular. As the disease progresses splenomegaly and to a lesser extent, hepatomegaly appear. *P. falciparum* infection is more serious than the others because of the high frequency of severe or fatal complications with which it is associated.

**B Laboratory Findings** The thick blood film, stained with Giemsa's stain or other Romanowsky stains, is the mainstay of malaria diagnosis. The thin film is used primarily for species differentiation after the presence of an infection is detected on a thick film. In all but *falciparum* infections the number of red cells infected seldom exceeds 2% of the total cells. Very high red cell infection rates may occur with *falciparum* infection (20-30% or more). For this reason anemia is frequently much more severe in *falciparum* malaria. The anemia is normocytic, with polikilocytosis and anisocytosis. During paroxysms there may be transient leukocytosis, leukopenia develops subsequently, with a relative increase in large mononuclear cells. During attacks hepatic function tests often become abnormal, but the tests revert to normal with treatment or spontaneous recovery. Hemolytic jaundice may develop in severe infections.

There are no specific blood chemical findings. In *P. malariae* infections a form of

nephrosis with protein and casts in the urine sometimes occurs in children. Severe falciparum infections may cause renal damage.

### Differential Diagnosis

Uncomplicated malaria particularly when modified by partial immunity must be distinguished from a variety of other causes of fever splenomegaly anemia or hepatomegaly. Some diseases often considered in the diagnosis of malaria in the tropics include genitourinary tract infections typhoid fever infectious hepatitis dengue kala azar influenza amebic liver abscess leptospirosis and relapsing fever. Examination of blood films is essential to differentiate atypical malaria from some of the above.

### Complications

Serious complications of malaria occur primarily in falciparum infections particularly in those persons who have experienced repeated attacks with inadequate treatment. These complications jointly referred to as pernicious malaria include cerebral malaria with headache convulsions delirium and coma hyperpyrexia closely resembling heat hyperpyrexia gastrointestinal disorders resembling cholera or acute bacillary dysentery and algid malaria which in certain respects resembles acute adrenal insufficiency. Black water fever must be considered apart from other falciparum complications. This acute intravascular hemolytic condition develops in patients with long standing falciparum infections and a history of irregular quinine dosage. The principal findings are profound anemia jaundice fever and hemoglobinuria. The mortality rate may be as high as 30% primarily due to anuria and uremia.

### A. Specific Measures

1. **Chloroquine** An effective agent against all forms of malaria and the treatment of choice for all forms of malaria during the acute attack. It will terminate *P. falciparum* infections and prevents relapses of vivax malaria when administered in conjunction with primaquine. Chloroquine causes few toxic symptoms when used in the doses given below. Mild headache pruritus anorexia blurring of vision malaise and urticaria may occur. If symptoms become severe stop the drug and give ammonium chloride 4 Gm (60 gr) stat and 1 Gm (15 gr) every 4 hours. Acidification promotes excretion of the drug.

(1) **Therapeutic dosage schedule** Give chloroquine phosphate (Aralen®) 1 Gm as initial dose 0.5 Gm in 6 hours and 0.5 Gm

daily for the next 2 days. In an emergency give chloroquine hydrochloride 0.2-0.3 Gm of base I.M. repeated in 6 hours if necessary and follow with oral therapy as soon as possible. It is not necessary to administer this drug I.V. since an effective blood level is rapidly attained by the I.M. route.

(2) **Suppressive dosage** Chloroquine di-phosphate 0.5 Gm weekly taken on the same day each week.

2. **Amodiaquin hydrochloride (Camoquin®)** is closely related to chloroquine chemically and pharmacologically. Toxicity is similar to that of chloroquine.

(1) **Therapeutic dosage schedule** Give 0.5 Gm of the base on the first day and then 0.4 Gm daily for next 2 days.

(2) **Suppressive dosage** 0.4 Gm of the base once weekly.

3. **Quinine** If none of the more effective and less toxic newer agents are available quinine is still a useful drug in arresting the acute attack of all types of malaria. Quinine in the following dosages may cause cinchonism (tinnitus vertigo deafness headache and visual disturbances) in some individuals. The possibility of black water fever arising during or at the cessation of therapy appears to be higher in quinine treated cases.

(1) **Therapeutic dosage schedule** Give quinine sulfate 0.6 Gm (10 gr) tid orally for 5-7 days or quinine dihydrochloride 0.65 Gm (10 gr) in physiologic saline glucose saline mixture or plasma. Caution. Inject I.V. very slowly (not more than 50 mg/minute) repeat in 6 hours if necessary and give no more than 3 injections in 24 hours. Quinine hydrochloride may also be administered by I.V. drip at the rate of 2 Gm (30 gr) in 24 hours. Follow with oral therapy as soon as possible.

(2) **Suppressive dosage** Quinine sulfate 0.3-0.6 Gm (5-10 gr) daily while in endemic area.

4. **Proguanil hydrochloride (Paludrine®)** although not an effective agent for the treatment of the acute clinical attack is a good suppressive drug for all forms of malaria. It has a tendency to provoke resistance. Toxicity is slight. Large doses cause nausea vomiting diarrhea and mild hematuria. Give 0.1 Gm daily or for partially immune subjects 0.3 Gm once weekly.

5. **Pyrimethamine (Daraprim®)** although not recommended for the treatment of acute clinical malaria is an effective agent for suppressive treatment. Suppressive cure is achieved against *P. falciparum* infection and sometimes against *P. vivax*. Toxicity is very low at the recommended dosage. Give 25 mg

weekly on the same day of each week. For children give 12.5 mg. weekly (may be dissolved in syrup).

6. Primaquine phosphate - This drug has been shown to be the most effective agent against the tissue forms of *P. vivax*, *P. malariae*, and *P. ovale* malaria. It is employed to eradicate the disease rather than to treat the clinical attack. It will prevent relapses in most cases. The patient must be observed carefully. Severe hemolytic reactions occur in some individuals, particularly Negroes. Watch for fall of hemoglobin or reduction in red count.

Dosage for the prevention of relapse is 26.3 mg. (15 mg. of base) daily in single or divided doses for 14 days. Treatment must be reinforced by standard treatment with chloroquine phosphate or amodiaquin if given during an acute attack.

B. General Measures. The nonspecific treatment of malaria is no different from that of any other acute febrile illness.

#### Prognosis.

The uncomplicated and untreated primary attack of vivax, ovale, or falciparum malaria usually lasts 2-4 weeks; that of malarise averages about twice as long (4-8 weeks). Each type of infection may subsequently relapse (once or many times) before the infection terminates spontaneously. Poorly treated or untreated falciparum malaria carries a less favorable prognosis than infections due to the other species because of the tendency to serious complications. When such complications as cerebral malaria and black-water fever develop, the prognosis is often poor even with treatment. With modern antimalarials the prognosis is good for most malaria infections, even with complications.

Crowther, A. F.: The chemotherapy of malaria. *J. Pharm. & Pharmacol.* 10:337-47, 1958.

#### SIMIAN MALARIA IN MAN

Recent developments have raised the possibility that enzootic malaria in monkeys may occasionally be transmitted to man (e.g., in Malaysia or the Philippines). Other species of *Plasmodium* may therefore soon be added to the 4 species recognized as characteristically infecting man.

#### AFRICAN TRYPANOSOMIASIS (Sleeping Sickness)

##### Essentials of Diagnosis.

- Inconspicuous local inflammatory reaction (trypanosomal chancre).
- Irregular fever, tachycardia, lymphadenitis, splenomegaly, transient rashes.
- Prolonged course (Gambian trypanosomiasis). Personality changes, headache, apathy, somnolence, tremors, speech and gait disturbances, anorexia, malnutrition, coma.
- Rapid course (Rhodesian trypanosomiasis). Findings as above, but lymph nodes less often enlarged.
- Death may occur before signs of CNS involvement appear.
- Trypanosomes in thick blood films or lymph node aspirates (early stages), CSF with trypanosomes, increased cells and protein (late stages).

In the tsetse fly regions of Africa trypanosomiasis should be suspected in patients with irregular fever and persistent tachycardia, particularly if the posterior cervical lymph nodes are enlarged. Final diagnosis depends on detection of the parasites in the blood or lymph nodes. Personality changes, headache, apathy, and somnolence suggest the possibility of CNS infection, confirmed by lumbar puncture. The diagnosis is seldom in doubt in the advanced stage of sleeping sickness.

##### General Considerations.

Rhodesian and Gambian trypanosomiasis are caused by 2 morphologically similar protozoan parasites, *Trypanosoma rhodesiense* and *T. gambiense*, found only as the mature trypanosome form in the blood stream, lymph nodes, myocardium, CSF, and brain. The disease occurs focally throughout tropical Africa. Both trypanosomes are transmitted by the bites of tsetse flies (*Glossina* sp.).

##### Clinical Findings.

A. Symptoms and Signs. The trypanosomal chancre, a local inflammatory reaction which appears about 48 hours after the tsetse fly bite, is the first sign of infection. Many patients give no history of such a reaction, in others the lesions are painful or pruritic and persist up to 3 weeks. The second stage, invasion of the blood stream and reticuloendothelial system, usually begins several weeks later.

Symptoms may appear at once particularly in rhodesiense infections or after several years. An irregular fever pattern with persistent tachycardia is characteristic. Transient rashes often circinate and scattered areas of firm edema may appear. There may be delayed sensation to pain with deep hyperesthesia. The spleen is usually enlarged. Enlarged rubbery and painless lymph nodes, particularly those of the posterior cervical group (Win terbottom's sign) are commonly found in gambiense infection. Lymph nodes are not of ten enlarged in rhodesiense infection. Signs of myocardial involvement appear early in Rhodesian trypanosomiasis. The patient may succumb to myocarditis before signs of CNS invasion appear. Manifestations of the final CNS stage appear within a few weeks or months of onset in rhodesiense infection. Gambian sleeping sickness differs from the acute and virulent Rhodesian form in that it develops more insidiously starting 6 months to several years from onset. Personality changes, spathy and headaches are among the early findings. Tremors, disturbances of speech and gait, mania, somnolence and anorexia appear late. The patient becomes severely emaciated and finally comatose. Death often results from secondary infection.

**B Laboratory Findings.** Lymph node puncture and examination of fresh and stained aspirates is the method of choice for finding *T. gambiense* prior to invasion of the CNS. In early rhodesiense infections blood films will usually reveal a few trypanosomes. In advanced cases lumbar puncture is necessary for diagnosis. The CSF which is clear, colorless and under normal pressure shows increased cells (lymphocytes) and elevated protein. Trypanosomes may be demonstrated in the centrifuged CSF specimen. Serologic tests are of little value in diagnosis.

Other laboratory findings include microcytic anemia, increased sedimentation rate, increased serum globulin and reduced total serum protein.

#### Differential Diagnosis

Trypanosomiasis may be mistaken for a variety of other diseases. Including malaria, kala-azar, cerebral tumors, encephalitis and cerebral syphilis. Serologic tests for syphilis may be falsely positive in trypanosomiasis. Malaria suggested by fever and splenomegaly may be ruled out by blood examinations, kala-azar considered because of irregular fever, anemia, splenomegaly, and lymphadenitis can usually be ruled out clinically without resorting to spleen or marrow

puncture. Other CNS conditions are differentiated by neurologic examination and lumbar puncture findings.

#### Prevention

Excretion of pentamidine isethionate and suramin sodium (see below) from the body is slow. Either drug will prevent infection for a considerable time after injection. A single injection of 1 Gm. of suramin will give protection for 6-12 weeks. One injection of pentamidine (4 mg./kg.) will protect against rhodesiense infection for 2 months and against gambiense infection for 3-6 months.

#### Treatment

##### A Specific Measures

1. Suramin sodium (Naphuride<sup>®</sup>, Antrypol<sup>®</sup>) is the drug of choice in the early stages of trypanosomiasis before the CNS is invaded. This organic urea compound is administered 1 V in freshly prepared 10% solution in distilled water. Start treatment with a test dose of 0.2 Gm. For adults continue with 1 Gm. doses at 5-7 day intervals to a total of 10 Gm. Because of occasional renal toxicity, frequent urinalyses are essential during therapy. Dermatitis and gastrointestinal disturbances are also reported. The drug is contraindicated in renal disease.

2. Pentamidine isethionate is a somewhat less effective alternative to suramin in treating early trypanosomiasis. It is administered as a 2% solution 1 V or 1 M. The drug may induce a sudden fall in BP or hypoglycemia. It is contraindicated in renal disease. Administer in doses of 4 mg./kg. daily or every other day for 10-15 injections.

3. Tryparsamide, a pentavalent arsenical, has long been used in the treatment of gambiense infections of the CNS. It is much less effective against rhodesiense meningoencephalitis. The drug may cause dermatitis or optic atrophy. Discontinue treatment if eye pain, excessive lacrimation or photophobia develops. Administer 1 V in a 20% solution in water. The dosage is 20-40 mg./kg. given at weekly intervals to a total dose of 10-20 Gm. The usual initial dose for adults is 1-1.5 Gm. subsequent doses 2-3 Gm. Repeat the course if necessary after a rest period of at least one month. A course of Bayer 205 or pentamidine should be given simultaneously to remove any parasites remaining in the blood or lymph nodes.

4. Melarsen oxide (Mel B<sup>®</sup>) is effective for the treatment of gambiense and rhodesiense infections of the CNS. It is nontoxic to the optic nerve and kidneys. Melarsen must be given 1 V in 5% solution in propylene glycol. A new



derivative, Mel W<sup>®</sup>, is water-soluble and may be given I.M. or subcut. It is necessary to use either suramin sodium or pentamidine isethionate in conjunction with melarsen to remove trypanosomes from the blood and lymph nodes. A recommended schedule is 3.6 mg./Kg. daily for 4 consecutive days, a rest for 7 days, and then a second series of 4 daily doses.

**B General Measures.** Good nursing care, treatment of anemia and concurrent infections and correction of malnutrition are essentials in the management of patients with advanced African trypanosomiasis.

### Prognosis.

Without treatment, 25-50% of gambiense infections and over half of rhodesiense infections are fatal. With treatment, 5-15% of gambiense infections and up to 50% of rhodesiense infections are fatal. Prognosis is considerably more favorable if treatment is started before invasion of the CNS occurs.

Buxton, P.A. Trypanosomiasis in Eastern Africa, 1947, H.M. Stationary Office, London, 1948.

Duggan, A.J. An approach to clinical problems of Gambian sleeping sickness. J. Trop. Med. 62: 268-74, 1959.

## AMERICAN TRYPANOSOMIASIS (Chagas' Disease)

### Essentials of Diagnosis

- Unilateral palpebral and facial edema and conjunctivitis (Romaña's sign)
- Hard, edematous, red and painful cutaneous nodule (chagoma)
- Intermittent fever, lymphadenitis, hepatomegaly, signs and symptoms of acute or chronic myocarditis or meningoencephalitis
- Demonstration of trypanosomes in blood smears or by culture, animal inoculation, or complement fixation test

Within the endemic regions, acute Chagas' disease in children is usually easy to diagnose. Chronic infection in adults, usually myocardial, is not clinically characteristic. Differentiation from other causes of chronic cardiac disease depends upon positive animal inoculation tests, complement fixation tests, or other laboratory procedures.

### General Considerations.

Chagas' disease is caused by *Trypanosoma cruzi*, a protozoan parasite of the blood and tissues of man and many other vertebrates. *T. cruzi* is found in wild animals from southern South America to northern Mexico, Texas, and the southwestern U.S. Human infection is less widespread. Many species of reduviid bugs (cone-nose or kissing bugs) transmit the infection, which results from rubbing infected bug feces, passed during feeding, into the bite wound. In the vertebrate host the trypanosomes first multiply close to the point of entry, assuming a leishmanial form at one stage of their development. They then enter the blood stream and later the heart, brain, and other tissues. Further multiplication causes cellular destruction, inflammation, and fibrosis. In these tissues the parasites again assume a leishmanial form during part of each developmental cycle.

### Clinical Findings

**A Symptoms and Signs.** The earliest finding in the acute infection is either the chagoma or Romaña's sign. In heavily endemic areas initial infection commonly occurs in childhood. The acute form of the disease may be fatal, particularly in infants and young children. In addition to intermittent fever, local lymphadenitis, and hepatomegaly, there may be splenomegaly, psychologic changes, focal neurologic symptoms, convulsions, tachycardia, cardiac enlargement, arrhythmias, and cardiac failure. Myocardial damage dominates the chronic form of the disease, cases are seen with all types and stages of cardiac disorder. Symptomatic chronic CNS infection is rare, also uncommon are megacolon and megasophagus, caused by damage to nerve plexuses in the bowel or esophageal wall.

**B Laboratory Findings.** Trypanosomes are not usually found in large numbers in the blood except in the early stages of the acute infection. *T. rangeli*, a nonpathogenic blood trypanosome also found in man in Central America and northern South America, must not be mistaken for *T. cruzi*. In the acute stage trypanosomes may also be found in lymph node aspirates. Blood, or material from lymph nodes, marrow, or spleen, may be cultured on NNN medium or inoculated into laboratory mice or rats. In chronic infections xenodiagnosis, which consists of permitting uninfected reduviids to feed on the patient and then examining them for trypanosomal infection, often establishes the diagnosis. The Machado complement fixation test is of presumptive diagnostic value when positive, it should be used in conjunction with other diagnostic methods.

**Differential Diagnosis**

The early acute infection with *Romana* sign might be confused with trichinosis but palpebral and facial edema is unilateral not bilateral and there is no eosinophilia. The chagoma may be mistaken for any of a variety of tropical skin lesions. Kala azar resembles Chagas disease in some respects (intermittent fever, hepatomegaly, splenomegaly) but in the former the spleen is much larger, there are no CNS symptoms and cardiac symptoms usually appear only after anemia becomes severe. Laboratory procedures may be necessary to rule out kala azar.

**Treatment**

No effective drug is available.

**Prognosis**

Acute infections in infants and young children are often fatal, particularly when the CNS is involved. Adults with chronic cardiac infections also may ultimately succumb to the disease. Mortality rates are not known because infections are often asymptomatic and unrecognized. Other infections, particularly malaria, may seriously complicate the disease.

Laranja F S & others. Chagas disease: a clinical, epidemiologic and pathologic study. *Circulation* 14: 1035-60, 1956.

**LEISHMANIASIS**

The 3 types of leishmaniasis are due to 3 species of protozoa related to the trypanosomes and transmitted by sandflies (*Phlebotomus* sp.) in which they undergo cyclic development from animal reservoirs (dogs and rodents). Visceral leishmaniasis (kala azar) is due to *Leishmania donovani*; cutaneous leishmaniasis (oriental sore) is due to *L. tropica*; and mucocutaneous or naso-oral leishmaniasis (espundia) is due to *L. braziliensis*.

Garnham P C C & D J Lewis. Parasites of British Honduras with special reference to leishmaniasis. *Tr. Roy. Soc. Trop. Med. & Hyg.* 53: 12-35, 1959.

Sen Gupta P C. Chemotherapy of leishmanial disease: a review of recent researches. *Indian Med. Gaz.* 85: 291-6, 1954.

Summary of Recent Abstracts. V. Leishmaniasis. *Trop. Dis. Bull.* 59: 509-13, 1962.

**1 VISCERAL LEISHMANIASIS (Kala-Azar)****Essentials of Diagnosis**

- Irregular fever, insidious and chronic onset may be acute.
- Progressive and marked splenomegaly and hepatomegaly.
- Progressive anemia, leukopenia and wasting.
- Progressive darkening of skin, especially on forehead and hands.
- Leishman-Donovan bodies demonstrable in splenic and sternal puncture smears.
- Nonspecific complement fixation test positive frequently and early.

Kala azar which is of subacute or acute onset resembles enteric fever (but there is no toxemia and Widal's test is negative) or malaria (in which case response to antimalarial therapy may aid the diagnosis, since concomitant malaria parasites may be present in the blood in kala azar). Many patients present with abdominal enlargement, weakness and wasting; these patients have irregular fevers and the spleen and liver are palpable, which differentiates this disease from brucellosis. Characteristic double (rarely triple) daily remissions (evening and morning) occur early.

Chronic cases may also be confused with infectious mononucleosis, leukemias, anemias due to other causes and tuberculosis. Post kala azar dermatitis may resemble leprosy.

**General Considerations**

Kala azar is widespread geographically wherever sandfly vectors are found. In each locale the disease has its own peculiar clinical and epidemiologic features. It occurs in the Mediterranean littoral, equatorial Africa, Ethiopia, eastern India, central Asia and China and South America. Although man is the major reservoir, animal reservoirs such as the dog are important. The incubation period varies from weeks to months. The parasites exist in one form in the body as oval Leishman-Donovan bodies which parasitize reticuloendothelial cells and lead to their proliferation. They are easily detected in the spleen, liver and bone marrow and may be found in blood.

### Clinical Findings.

**A. Symptoms and Signs** The fever is generally mild and is not usually associated with prostration. The characteristic double daily remission may escape detection. The spleen usually enlarges much more than the liver and may be palpable by the second month. Enlargement is painless, steady, and rapid, usually in waves with bouts of fever. At first doughy, the spleen finally becomes large and hard. Wasting occurs without anorexia.

**Post-kala-azar dermal leishmaniasis** may appear 1-2 years after apparent cure, especially in India but also in the Sudan and China. This may simulate leprosy as multiple hypopigmented macules or nodules which develop on pre-existing lesions. There may even be a degree of leontiasis. They may take the form of erythematous patches, often on the face.

**B. Laboratory Findings.** There is usually progressive gross leukopenia (seldom over 3000/cu. mm. after the first 1-2 months), with relative or (usually) absolute monocytosis. Nevertheless, an occasional leukocytosis, due to concurrent sepsis, may be confusing. Diagnosis must always be confirmed by demonstrating Leishman-Donovan bodies in blood, sternal marrow, liver, or spleen. Blood culture is highly successful, and a nonspecific complement fixation test has been devised which is often positive in the first month but is meaningless in the presence of chronic pulmonary tuberculosis. Diagnosis may be supported by a positive formol-gel test, in which a drop of commercial formalin in 1 ml. of serum produces opacity in 2 hours.

### Treatment.

General treatment must include a diet rich in protein and vitamins. Specific treatment is primarily with pentavalent antimonials, to which cases from India respond best whereas those from the Sudan are most resistant. Children tolerate antimonials well. In all cases resistance to antimonials can develop with inadequate dosage. In addition to antimonials, aromatic diamidines (see below) are powerful agents. They should be preceded by injection of epinephrine or an antihistaminic to minimize reactions. They are less effective for post-kala-azar dermal lesions. Fresh solutions only should be given and ampules stored away from heat. I.V. injection must be given slowly.

(1) Sodium antimony gluconate (Pentostam<sup>®</sup>, Solustibosam<sup>®</sup>, Stibinol<sup>®</sup>), 0.2 Gm. followed by 0.3 Gm. daily as 5% solution I.V. for patients weighing over 30 Kg. Continue treatment for 6-15 days.

(2) Stilbamidine isethionate is used only in antimony-resistant cases and must be given with great care because it is unstable and may produce immediate reactions or delayed trigeminal hyperesthesia. The initial adult dose is 25 mg. I.V. daily, increasing by 10-20 mg. daily to 2 mg./Kg. daily. The most that should be given is about 10 injections or a total of about 15 mg./Kg.

(3) Ethylstibamine (Neostibosam<sup>®</sup>), dosage as above, I.V.

(4) Ures stibamine (carbo-stibamide), I.V. in 10 ml. water daily, in doses of 0.05, 0.1, 0.15, and subsequently 0.2 Gm. for about 15 days.

(5) Pentamidine isethionate (Lomidine<sup>®</sup>), preferably I.M., 4 mg./Kg. daily or on alternate days, up to 15 injections.

### Prognosis.

Therapy is effective but there may be relapses. Keep the patient under observation for at least 6 months. The spleen, blood picture, and body weight should return to normal. Splenectomy before repetition of a course of treatment may be advisable in refractory cases.

See references on p. 688.

## 2. CUTANEOUS LEISHMANIASIS (Oriental Sore)

Cutaneous swellings follow the bites of sandflies infected with *Leishmania tropica* after an interval of weeks or even years. Oriental sore is widespread in distribution, including Latin America. The swellings may ulcerate and discharge pus, or they may remain dry. Dry and moist forms are caused by locally distinct leishmanias.

Lesions tend to heal spontaneously, but secondary infection may lead to gross extension. Moist ulcerated lesions are covered with a scab and exude purulent material as a result of secondary infection.

Leishmanias cannot be detected in purulent discharge but may be seen in scrapings from the cleaned edge. Needle biopsy material from the edge can be cultured in NNN medium.

Single lesions may be cleaned, curetted, covered, and left to heal. Antibiotics may be required for secondary infection. Ethylstibamine (Neostibosam<sup>®</sup>) as for visceral leishmaniasis (10-12 injections) is effective.

Langsjoen, P.H.: Cutaneous leishmaniasis: a report of 10 cases. *Ann. Int. Med.* 45: 523-39, 1956. See also references on p. 688.

### 3. MUCOCUTANEOUS (NASO-ORAL) LEISHMANIASIS (Espundia)

Espundia is a chronic infection, caused by *L. braziliensis*, which occurs principally in Brazil, Paraguay, and Peru. It is characterized by cutaneous and naso-oral involvement, either by direct extension or, more often metastatically. The initial lesions on exposed skin, often the ears, take more varied forms than is usual with Oriental sore. Naso-oral involvement may follow healing of lesions, even after a considerable interval, or may develop simultaneously. The anterior part of the cartilaginous septum is commonly involved, and there may be gross and hideous erosion, including bone. Regional lymphadenitis is common. Leishman-Donovan bodies may be found in aspirated tissue-jucose, and leishmanias may be cultured. If an injection of a suspension of killed leptomonads produces a fully developed papule in 2 days which disappears after a week (positive Montenegro's test), the diagnosis is fairly certain. A negative Montenegro's test is meaningless.

Specific treatment may be combined, if necessary, with local or systemic antibiotics or sulfonamides. Give antimony potassium tartrate, 100 mg (1½ gr.) I.V. on alternate days for up to 15 injections, repeat if necessary. Ethylstilbamine (Nostibosam®) may be given as for visceral leishmaniasis.

See references on p. 688

### GIARDIASIS (Lambliasis)

*Giardia lamblia* is a cosmopolitan intestinal flagellate protozoan which normally lives in the duodenum or jejunum and is usually of low pathogenicity or nonpathogenic for man. Cysts may be found in large numbers in the stools of asymptomatic persons. In some people, however, heavy *Giardia* infection seems to cause irritation of the upper small bowel with resultant acute or chronic diarrhea, mild abdominal cramps, flatulence, abdominal distention, and constipation. The bile ducts and gallbladder may be invaded, causing a mild cholecystitis. The distinctive cysts may be found in formed stools, and cysts and trophozoites may be found in liquid stools.

Treatment with quinacrine hydrochloride (Atsbrine®), 0.1 Gm. (1½ gr.) orally t i d for 5 days will result in a 90% cure rate. The treatment may be repeated if necessary.

Culbertson, J. T.: Chemotherapy of intestinal parasitic infections. *M. Clin. North America* 40 532, 1956.

Webster, B. H.: Human infection with *Giardia lamblia*. *Am. J. Digest. Dis.* 3 64-70, 1958.

### BALANTIDIASIS

*Balantidium coli* is a large ciliated intestinal protozoan found throughout the world particularly in the tropics. Infection results from ingestion of viable cysts from formed stools of humans or swine, the reservoir hosts. In the new host the cyst wall dissolves and the trophozoite may invade the mucosa and submucosa of the large bowel and terminal ileum causing abscesses and irregularly rounded ulcerations. Many cases are asymptomatic. Chronic recurrent diarrhea, alternating with constipation, is the most common clinical manifestation, but attacks of severe dysentery with bloody mucoid stools, tenesmus, and colic may occur intermittently. Diagnosis is made by finding trophozoites in liquid stools and cysts in formed stools. No specific chemotherapy is consistently successful. The tetracycline antibiotics are claimed to be specific, but the number of successfully treated cases is small. Carbarsone, diiodohydroxyquin (Diodoquin®), iodothydroxyquin (Vioform®), and acetarsone (Stovarol®) have each been effective in a few patients. Asymptomatic infections may terminate spontaneously. In properly treated mild to moderate symptomatic cases the prognosis is good, but severe infections are sometimes fatal despite treatment.

Ares, V. M.: Balantidiasis. A review and report of cases. *Am. J. Path.* 32 1089-15, 1956.

### TOXOPLASMOSIS

The protozoan parasite *Toxoplasma gondii* is found throughout the world in man and in many species of animals. The mechanism of transmission of the organism is not known. The organism lives both intracellularly and extracellularly in the reticulo-

endothelial system, parenchymal cells, and exudates. Symptomatic infection is rare in adults, the active infection is most often encountered in the newborn, who acquire their infection in utero. Infants and young children may have hydrocephaly or macrocephaly, psychomotor disturbances, cerebral calcifications, and chorioretinitis. In acquired infections of adults there may be fever, malaise, arthralgia, maculopapular rash and lymphadenopathy, conjunctivitis, and myocarditis. Toxoplasma organisms may be directly identified in smears of blood, bone marrow, CSF, or exudates. Inoculation into laboratory animals or serologic tests, including the Sabin-Feldman dye test, complement fixation tests, and neutralization tests are often necessary for diagnosis. The skin test is primarily a survey tool and is of little diagnostic value. There is no effective treatment, although combined sulfadiazine and pyrimethamine (Daraprim®) therapy has shown some promise. The congenital disease is often fatal, and if the infant survives the acute infection he is likely to be handicapped by serious residual CNS and ocular lesions. The acquired disease is usually asymptomatic or mild, but acute infection in adults may be fatal.

Frankel, J.K., & others. Acute toxoplasmosis, effective treatment with pyrimethamine,

sulfadiazine, leucovorin calcium and yeast, J.A.M.A. 173 1471-6, 1960.  
Remington, J.S., Jacobs, L., & H.E. Kaufman. Toxoplasmosis in the adult. New England J. Med. 262:180-6 and 237-41, 1960.

### COCCIDIOSIS (Isosporosis)

Two cosmopolitan intestinal species of coccidia, *Isospora belli* and *Isospora hominis*, are found in man. The infection is usually sporadic and is most common in the tropics and subtropics, although it has been reported in the U.S. Infections result from the ingestion of viable cysts, and it is probable that the protozoa multiply in the intestinal mucosa. Many cases may be asymptomatic. About one week after ingestion of viable cysts, mild fever, lassitude, and malaise may appear, followed by mild diarrhea and vague abdominal discomfort. The infection is self-limited and symptoms usually subside within 1-2 weeks. Stool concentration techniques are usually necessary to find the immature oocysts of *I. belli* or the mature sporocysts of *I. hominis*. Bed rest and a bland diet for a few days is the only treatment necessary.

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## Infectious Diseases: Metazoal

Frederick L. Dunn & J. Ralph Audy

### TREMATODE (FLUKE) INFECTIONS

#### SCHISTOSOMIASIS (Bilharziasis)

##### Essentials of Diagnosis.

- Transient pruritic petechiae on skin recently exposed to fresh water
- Fever, malaise, nausea, urticaria, and eosinophilia.
- Either (1) diarrhea, dysentery, abdominal pain, anorexia, weight loss, splenomegaly, and ascites, or (2) terminal hematuria, urinary frequency, urethral and bladder pain

Early intestinal schistosomiasis may be mistaken for amebiasis, bacillary dysentery, or other causes of diarrhea and dysentery. Later the various causes of portal hypertension or of bowel papillomas and polyps must be considered. Vesical schistosomiasis must be differentiated from other causes of hematuria, prostatic disease, genitourinary tract malignancies, and bacterial infections of the urinary tract.

##### General Considerations.

Three blood flukes or trematodes are responsible for this world-wide complex of diseases. *Schistosoma mansoni*, the cause of intestinal schistosomiasis, is widespread in Egypt and is common locally in tropical Africa, eastern South America, and the Caribbean (including Puerto Rico). Vesical or urinary schistosomiasis, caused by *S. haematobium*, is common in Egypt and in Africa and parts of the Middle East. Asiatic intestinal schistosomiasis, due to *S. japonicum* infection, is important in China, Japan, and the Philippines. Various species of snails, the intermediate hosts, are infected by larvae hatched from

eggs reaching fresh water in feces or urine. After development infective larvae (cercariae) leave the snails and penetrate human skin or mucous membranes which come in contact with water. Immature *S. mansoni* migrate to branches of the inferior mesenteric veins in the large bowel wall. Here the adults mature, mate, and deposit eggs. Many eggs reach the bowel lumen and are passed in the feces; others lodge in the bowel wall and induce inflammation, fibrosis, ulceration, and granuloma, papilloma, or polyp formation. Eggs may be carried to the liver, where similar changes occur, provoking periportal cirrhosis. Diffuse hepatic cirrhosis in advanced cases is probably due to associated nutritional deficiency. Portal hypertension results in splenomegaly and ascites. Eggs may lodge ectopically in the lungs, spinal cord, or other tissues.

*S. japonicum* adults lie in branches of the superior and inferior mesenteric veins in the small and large bowel walls. Eggs are passed in the stool or lodge in the bowel wall, provoking changes similar to those noted above. Because greater numbers of eggs are produced by *S. japonicum*, the resulting disease is more extensive and severe. Eggs are frequently carried to the liver and occasionally to the CNS. Cirrhosis and portal hypertension are common as the immature flukes migrate through the blood vessels of various organs.

The adult *S. haematobium* matures in the venous plexuses of the bladder, prostate, and uterus. Eggs are passed in the urine or retained in the tissues, particularly the bladder wall and the female genital organs. In addition to fibrosis, ulceration, and granuloma and papilloma formation, there is often bladder wall calcification, chronic cystitis, pyelitis, or pyelonephritis. Bladder cancer is common in advanced cases in Egypt.

##### Clinical Findings.

**A. Symptoms and Signs.** The first sign of infection, an itchy petechial rash at sites of penetration of cercariae, lasts no more than 2-3 days. A second clinical stage occurs 4-5 weeks later as the immature flukes migrate through

the blood vessels of various organs. Symptoms at this time are primarily allergic and vary greatly in severity. In addition to fever, urticaria, malaise, and respiratory symptoms, the liver and spleen may be temporarily enlarged. The patient again becomes asymptomatic in 2-8 weeks. The final clinical stage begins 6 months to several years after infection as lesions develop around eggs imbedded in the tissues. The course and severity of the disease depend upon the number of adult worms present, the number of eggs produced, and the sites of the lesions they provoke. Diarrhea, dysentery and abdominal pain are common in the early stages of intestinal infections. Anorexia, weight loss, polypoid intestinal tumors and signs of portal hypertension and hepatic insufficiency appear as the disease progresses. Death commonly results from intercurrent infection. The symptoms of urinary tract disease (particularly terminal hematuria, frequency and pain) depend upon the extent of the pathologic changes described above. Ureteral and renal damage may result in fatal uremia, or the patient may die of bladder carcinoma many years after first being infected. Advanced schistosomiasis usually develops only after repeated reinfections.

**B Laboratory Findings.** Eosinophilia is common during the migrations of the immature flukes, but the count usually returns to normal later. Diagnosis depends upon detection of eggs in urine or feces, on biopsy techniques, or on serologic and skin tests. In urine eggs are found most easily by examining the terminal drops, preferably after the patient has exercised, or the sediment of a 24-hour urine collection. Eggs may be found in stool specimens by direct examination, but some form of concentration is usually necessary and repeated examinations are often needed to find eggs in light infections. *S. mansoni* infections are often diagnosed by rectal biopsy, biopsy through a cystoscope may confirm the diagnosis of urinary schistosomiasis. The complement fixation test becomes positive a few weeks after infection occurs and may remain so for several years. Few infected persons give negative reactions. The intradermal test is less valuable for clinical purposes.

### Complications

Among the many complications of these diseases are transverse myelitis (*S. mansoni* eggs in the spinal cord), seizures, optic neuritis, paralysis, mental disorders (*S. japonicum* eggs in the brain), liver failure (*S. mansoni*, *S. japonicum*), ruptured esophageal varices due to portal hypertension, uremia

and bladder neoplasms (*S. haematobium*) and chronic pulmonary disease (periarteritis and endarteritis, primarily due to *S. mansoni* eggs).

### Treatment.

**A. General Measures.** For patients with long-standing schistosomiasis and nonreversible lesions, supportive measures, improvements in diet, and corrective surgical procedures are usually more important than specific chemotherapy. Such therapy may even be dangerous in cases with hepatic insufficiency. At best drugs prevent further progression and the development of complications. Surgical measures include removal of papillomas, polyps and early carcinoma, splenectomy, portal shunt operations, craniotomy, and other neurosurgical procedures.

**B. Specific Measures.** In less advanced disease drug therapy often causes clinical cure, i.e., relief of symptoms and shrinking or elimination of bladder and bowel ulcerations and granulomas. Periodic laboratory follow-up is essential for at least 6 months.

1. Antimony potassium (or sodium) tartrate is an inexpensive and effective but highly toxic drug. The patient must be at bed rest during treatment. Start with 30 mg ( $\frac{1}{2}$  gr) in a 1-2% solution in 5% glucose or normal saline. Administer slowly I/V with care to avoid leakage (to prevent tissue sloughing). On the second day increase the dose to 60 mg (1 gr), on the third day to 90 mg ( $1\frac{1}{2}$  gr) and on the fourth day to 120 mg (2 gr).

A total of 1.8 Gm (27 gr) is usually adequate for *S. haematobium* infections, for both forms of intestinal schistosomiasis, use a total dose of 2.4 Gm (36 gr). For *S. haematobium* infections a short intensive course of treatment is often effective. Give 60 mg (1 gr)/12 lb body weight divided into 6 doses I/V over a period of 3-6 days.

Common side effects include nausea, vomiting, diarrhea, abdominal pain, syncope, tachycardia, dyspnea, paroxysmal coughing and erythematous rashes. More severe toxic effects include exfoliative dermatitis, toxic liver necrosis, and toxic myocarditis. Cardiac, pulmonary, renal, hepatic, CNS, and febrile diseases are contraindications.

2. Stibophen (Fusidin®) is less effective but far less toxic than antimony potassium tartrate. Only pulmonary and renal disease contraindicate its use. It may be given I.M., an advantage with children and debilitated patients. It is supplied in 5 ml ampules of a 7% solution. Use 1.5 ml the first day, 3.5 ml the second, 5 ml the third, and then continue with 5 ml every other day to a total dose



of 40-50 ml. This course may be repeated if necessary. Fuadin® is often effective in urinary schistosomiasis and occasionally effective in *S. mansoni* and *S. japonicum* infections.

3. Lucanthone hydrochloride (Miraclil D®, Nilodin®) is administered orally and is thus suitable for mass treatment. Numerous side effects include giddiness, vertigo, tremors, epigastric pain, vomiting, diarrhea, insomnia, and muscular weakness. Cardiac and renal disease are contraindications. The total dose is 50-75 mg. (1-1 1/4 gr.)/Kg. body weight given in divided doses over a period of 3-5 days. The drug provides symptomatic relief in *S. haematobium* infections and cures up to 60% of cases. It is much less effective for *S. mansoni*, and is of no value for *S. japonicum*.

#### Prognosis.

With treatment the prognosis is good in early and light infections if reinfection does not occur. In advanced disease with extensive involvement of the intestines, liver, bladder, or other organs, the outlook is poor even with treatment.

Bilharziasis (papers by various authors). Bull. World Health Organ. 18 685-1116, 1958.

### FASCIOLOPSIASIS

The large intestinal fluke, *Fasciolopsis buski*, is a common parasite of man and pigs in China, Formosa, Indochina, Assam, and Bengal. When eggs shed in stools reach water they hatch to produce free-swimming larvae which penetrate and develop in the flesh of snails. *Cercariae escape from the snails and encyst on various water plants. Man is infected by eating these infected plants, usually water chestnuts or caltrops, uncooked. Adult flukes, mature in about 3 months, live in the small intestine attached to the mucosa or buried in mucous secretions.*

After an incubation period of several months manifestations of gastrointestinal irritation appear in all but light infections. Symptoms in severe infections include cramping, epigastric and hypogastric pains, diarrhea, intermittent constipation, anorexia, and nausea. Ascites and edema, particularly of the face, may occur later, apparently as a result of absorption of toxic metabolic products of the worms. Death may result from cachexia or intercurrent infection.

Leukocytosis with moderate eosinophilia is common. The diagnosis depends upon discov-

ery of eggs, or occasionally flukes, in the stools.

Crystalline hexylresorcinol (Crystoids Anthelmintic®, Caprokol®) is the most effective drug. For adults give 1 Gm (15 gr.) orally in 0 1-0 2 Gm. (1 1/2-3 gr.) capsules on an empty stomach in the morning. For children, give 0 1 Gm (1 1/2 gr.)/year of age to age 10. A light supper and purgation on the previous evening with sodium sulfate is desirable. Two hours after administration, repeat purgation with sodium sulfate. Repeat treatment in 3-4 days. Two courses are usually sufficient, occasionally 3 or more courses may be necessary. For somewhat greater effectiveness administer the drug transduodenally, 1 Gm (15 gr.) in 20 ml of water.

Tetrachloroethylene may be used if hexylresorcinol is not effective or not available. Administer as for hookworm disease.

Heavy infections with severe toxemia may be fatal, particularly in children, in spite of treatment to remove the flukes. In all other cases, with treatment, the prognosis is good.

McCoy, O.R., & T.C. Chu: Fasciolopsis buski infection among school children in Shaohsing, and treatment with hexylresorcinol. Chinese M.J. 51, 937-44, 1937.

### CLONORCHIASIS

Infection by *Clonorchis sinensis*, the liver fluke, is endemic in parts of Japan, Korea, China, Formosa, and Indochina. Imported cases are seen in the United States. Certain snails are infected as they ingest eggs shed into water in human or animal feces. Larval forms escape from the snails, penetrate the flesh of various freshwater fish, and encyst. Human infection results from eating such fish, either raw or undercooked. In man the ingested parasites encyst in the duodenum and ascend the bile ducts into the biliary capillaries where they lodge and mature. The adults remain in the liver throughout their lives, shedding eggs in the bile. Biliary epithelial hyperplasia and fibrosis develop around the worms. In heavy infections eggs may lodge in the liver parenchyma, causing granulomatous reactions.

Most patients harbor few worms and remain permanently free of symptoms from the time of infection. In some cases, with heavy infection, immature flukes migrating into the biliary capillaries may cause malaise, fever, liver tenderness, and jaundice. These symp-

toms are transient. With heavy infection symptoms later reappear after the flukes have matured. Progressive liver enlargement, tenderness, and right upper quadrant pain are the common findings. Vague abdominal symptoms, diarrhea, weakness, weight loss, jaundice, tachycardia, and a variety of other findings have been attributed to advanced clonorchiasis.

During the stage of invasion by the immature flukes there is often eosinophilia of 10-40% later the count usually falls to normal. In advanced disease liver function tests will indicate parenchymal damage, the first test to become abnormal as the disease progresses is usually that for urine urobilinogen. Eggs may be found for diagnosis in the stools or duodenal aspirates.

There is no satisfactory specific drug. Treatment is primarily symptomatic and supportive. Gentian violet, tartar emetic, and other drugs have produced only equivocal results. Chloroquine may be of some value. Although it apparently does not kill the flukes or flush them out of the bile capillaries, it often reduces or stops the egg output, and may provide symptomatic relief. The adult dosage is 300 mg (5 gr) of the base orally b i d for 4-8 weeks. The longer course is usually necessary. Side reactions (nausea, anorexia, headache, pruritus, dizziness) in the first 2 weeks of therapy are common and may require temporary reduction of dosage, later these symptoms usually subside.

Clonorchiasis is rarely a fatal disease in itself, but patients with advanced infections and impaired liver function may succumb more readily to other diseases. The prognosis is good for light to moderate infections.

Ehrenworth, L., & R.A. Daniels. Clonorchiasis sinensis. Clinical manifestations and diagnosis. *Ann. Int. Med.* 49:419-27, 1958.

## PARAGONIMIASIS

*Paragonimus westermani*, the lung fluke, commonly infects man throughout the Far East, and locally in West Africa and northern South America. Other mammals may serve as alternate hosts for the adult flukes. Eggs reaching water, either in sputum or feces, hatch in about 3 weeks. The larvae penetrate snails, develop, and emerge as cercariae which encyst in the tissues of crayfish and crabs. When these crustaceans are eaten raw, immature flukes excyst in the small intestine and penetrate into the peritoneal cavity. Most migrate

through the diaphragm and enter the peripheral lung parenchyma, some may lodge and mature in the peritoneum, the intestinal wall, and the liver, or other tissues. Rarely they may migrate to the brain or spinal cord. A capsule of fibrous and inflammatory tissue forms around the parasite as it matures. Later the capsule swells and ruptures into a bronchiole. Fluid containing eggs, blood, and inflammatory cells is released and expectorated in the sputum.

The infection is asymptomatic until the flukes mature and begin producing eggs. The insidious onset is marked by low-grade fever, cough, or hemoptysis. The cough is dry at first, later it becomes productive of viscous sputum, rusty or blood-flecked. Pleuritic chest pain is common. The condition is chronic and slowly progressive. Dyspnea, signs of bronchitis and bronchiectasis, weakness, malaise, and weight loss are apparent in heavy infections. Many patients with light infections do not appear seriously ill. Parasites in the peritoneal cavity or intestinal wall may cause abdominal pain, diarrhea, or dysentery. Those in the CNS, depending upon their location, may give rise to seizures, palsies, or meningoencephalitis.

Slight leukocytosis and eosinophilia are common. The sputum may contain eosinophils and Charcot-Leyden crystals in addition to blood and eggs. Eggs are more readily demonstrated by examining smears of centrifuged sodium hydroxide-treated sputum sediment. Eggs are also found in stool specimens, particularly after concentration. Skin and complement fixation tests are used as aids in diagnosis in some Far Eastern countries.

No satisfactory specific drug is available. Emetine hydrochloride in doses of 40-80 mg (2/3-1 1/4 gr) i M daily for 10 days, may relieve symptoms and kill the flukes in some patients. This course may be repeated after a 2-3 week interval. Chloroquine is probably somewhat more effective, using the dosage as for clonorchiasis. Aside from a trial with one of the above, treatment is symptomatic and supportive. Antibiotics may be necessary to control secondary pulmonary infection.

Barring reinfection, light to moderate infections subside spontaneously in 6-7 years and require little treatment. Heavy infections may be progressive for years, even without reinfection, and may be eventually fatal particularly if there is concurrent tuberculosis. The prognosis is unfavorable for the rare CNS infections.

Harter, D.H., & S.I. Morse. Pulmonary paragonimiasis: report of a case. *Ann. Int. Med.* 51:1104-8, 1959.

## CESTODE INFECTIONS

### TAPEWORM INFECTIONS (See Also Echinococcosis)

#### Essentials of Diagnosis

- Finding of segments in clothing or bedding
- Most infections asymptomatic, occasionally diarrhea or vague abdominal pains.
- Characteristic eggs or segments in the stool
- Rarely (in cysticercosis), seizures, mental deterioration, signs and symptoms of internal hydrocephalus

The diagnosis of adult tapeworm infections ordinarily depends upon identification of segments or eggs. Fish tapeworm infections may occasionally be recognized through discovery of a macrocytic anemia resembling pernicious anemia. Cerebral cysticercosis may produce a variety of clinical manifestations, many other causes of seizures mental deterioration or internal hydrocephalus may be considered before the diagnosis is finally made.

#### General Considerations

A number of species of adult tapeworms have been recorded as human parasites, but only 6 infect man frequently. *Taenia saginata*, the beef tapeworm, and *T. solium* the pork tapeworm, are cosmopolitan and common. The fish tapeworm, *Diphyllobothrium latum* is most often found in northern Europe, Japan and the Great Lakes region of the United States. The dwarf tapeworms *Hymenolepis nana* and *H. diminuta*, are cosmopolitan throughout the tropics and subtropics. The dog tapeworm, *Dipylidium caninum*, is occasionally reported in children in Europe and North America.

The adult tapeworm consists of a head (scolex), which is a simple attachment organ, a neck, and a chain of individual segments (proglottids). While *Hymenolepis nana* adults are rarely more than 2.5-5 cm (1-2 inches) long, beef, pork, and fish tapeworms often exceed 10 feet in length. Gravid segments detach themselves from the chain and escape from the host intact, or rupture, releasing eggs in the feces. In the case of *T. saginata*, the most common tapeworm found in man in the

United States, eggs are expelled from the segments after they pass from the host. The eggs hatch when ingested by cattle, releasing embryos which encyst in muscles as cysticerci. Man is infected by eating undercooked beef containing viable cysticerci. In the human intestine the cysticercus develops into an adult worm.

The life cycle of *T. solium* is similar except that the pig is the normal host of the larval stage. Man may be infected by the larval pork tapeworm however, if he accidentally ingests *T. solium* eggs. As in the pig, the larvae find their way to many parts of the body and encyst as cysticerci. Only those lodging in the brain ordinarily produce symptoms (cerebral cysticercosis).

The intermediate hosts of the fish tapeworm are various species of fresh water crustaceans and fish. Eggs passed in human feces are taken up by crustaceans which are in turn eaten by fish. Human infection results from eating raw or poorly cooked fish.

The *H. nana* life cycle is unusual in that both larval and adult stages of the worms are found in the human intestine. Adult worms expel eggs in the intestinal lumen. Newly hatched larvae invade the mucosa, where they develop for a time before returning to the lumen to mature. *H. nana*, requiring no intermediate host, can be transmitted directly from man to man. A similar dwarf tapeworm *H. diminuta* is a common parasite of rodents. Many arthropods, such as rat fleas, beetles and cockroaches, serve as intermediate hosts. Man is infected by accidentally swallowing the infected arthropods, usually in cereals or stored products. Multiple dwarf tapeworm infections are the rule, whereas man rarely harbors more than one or two of the larger adult tapeworms.

*Dipylidium caninum* infections generally occur in young children living in close association with infected dogs or cats. Transmission results from swallowing the infected intermediate hosts, fleas or lice.

#### Clinical Findings

**A Symptoms and Signs.** Adult tapeworms in the human intestine ordinarily cause no symptoms. Occasionally weight loss or vague abdominal complaints may be associated with heavy infections or large worms. Heavy infections with *H. nana* may, however, cause diarrhea, abdominal pain, anorexia, weight loss, and nervous disturbances, particularly in children. In 1-2% of those harboring the fish tapeworm, a macrocytic anemia of considerable severity may be found. The anemia may be accompanied by glossitis, lethargy,

and signs of nerve damage. In cysticercosis most larval tapeworms lodge in muscles or connective tissues where they remain silent and eventually calcify, in the brain, however, they may cause a wide variety of manifestations. Epileptic seizures, mental deterioration, personality disturbances, and internal hydrocephalus with headache, giddiness, papilledema, and nerve palsies are among the more common consequences of brain involvement.

**B. Laboratory Findings.** Infection by a beef tapeworm is often discovered by the patient when he finds one or more segments in his clothing or bedding. To determine the species of worm such segments must be flattened between glass slides and examined microscopically. Most tapeworm infections are detected by laboratory examination of stool specimens for eggs and segments. In cysticercosis x-rays often reveal calcified cysticerci in muscles, but those in the CNS rarely calcify and cannot be seen radiologically. When cysticerci lodge in the fourth ventricle the CSF pressure may be abnormal, and the fluid may show increased numbers of mononuclear cells and tapeworm scolices. Skin and complement fixation tests are also available as aids in diagnosis of cysticercosis.

When fish tapeworm macrocytic anemia is discovered, the marrow will be found to be megaloblastic, and hydrochloric acid is usually present in the stomach. This anemia is attributed to the affinity of the worm for dietary vitamin B<sub>12</sub>.

### Differential Diagnosis

Since most tapeworm infections are asymptomatic, a differential diagnosis need rarely be considered. When vague abdominal complaints and weight loss are present stool examinations are essential to rule out other forms of intestinal parasitism and primary gastrointestinal disorders. Fish tapeworm anemia may mimic pernicious anemia but the presence of gastric hydrochloric acid and positive stool examinations will establish the diagnosis.

### Complications

Pork tapeworm infection may be complicated by cysticercosis if the patient unwittingly contaminates his hands with eggs and transfers them to his mouth. For such a patient vomiting is also a hazard in that eggs may be propelled up the small intestine into the stomach, where they may hatch. The macrocytic anemia occasionally associated with *D. latum* infection also constitutes a potentially serious complication.

### Treatment.

#### A. Specific Measures

**1 Quinacrine hydrochloride (Atabrine<sup>®</sup>)** is the drug of choice. On the day preceding treatment the patient should have only a liquid diet, with nothing but water or milkless tea or coffee for supper. On the evening before treatment, give a saline purge or a soap-suds enema. On the morning of treatment, withhold breakfast and confine the patient to bed. Give chlorpromazine (Thorazine<sup>®</sup>), phenobarbital, or a similar sedative to prevent vomiting. One hour later, give quinacrine in the range of 0.5 Gm (7½ gr.), for children weighing 40-75 lb., to 1 Gm (15 gr.) for adults or children weighing over 100 lb. The dose may be divided to reduce the risk of vomiting but all of it must be given within about 30 minutes. Administer quinacrine by duodenal tube if the patient persistently regurgitates the drug.

Two hours later (2 hours after the last dose, if divided doses are given), repeat the saline purge. No food should be permitted until the bowels move copiously.

Cure depends upon death or evacuation of the head (scolex). Evacuations should be collected in a basin of warm water, and toilet paper must be disposed of separately to allow search for the head and proglottids. If no head is found, continue to examine the stools for eggs or proglottids once a month for 6 months. Repeat treatment if stools become positive.

**2 Aspidium oleoresin.** This drug is contraindicated in severe cardiac, hepatic, or renal disease, constipation, acute or chronic gastroenteritis, febrile states, pregnancy, and infancy. Give a low-residue, fat-free diet for 24-48 hours before therapy. Alcohol is contraindicated. Magnesium sulfate or sodium sulfate, 15-30 Gm (¼-1 oz.) in water is given the night before treatment. Withhold breakfast on the morning of treatment. Administer oleoresin of aspidium in gelatin capsules in 3 equal doses at half-hour intervals each dose containing from 0.6-1.2 Gm (10-20 gr.) depending upon the weight of the patient. Children should receive 1 minims/year of age. (Note: The drug should be fresh, not dispensed from bottles which have been opened for some time.) Magnesium sulfate or sodium sulfate, 15-30 Gm (¼-1 oz.) in water is given again 2 hours after administration of the last capsule. No food should be permitted until the bowels move copiously.

Repeat course of treatment in not less than 7 days if necessary.

Alternate method of administration of oleoresin of aspidium

2 Aspidium oleoresin	4 ml	(1 dr)
Mucilage of acacia	30 ml.	(1 oz)
Concentrated solution of sodium sulfate	30 ml.	(1 oz.)

Give this emulsion orally or by duodenal tube in one administration. Post-treatment purgation is not necessary.

One-half the dosage is satisfactory for children of school age.

Attend to stools and to follow-up as above.  
3 Hexylresorcinol - Give 1 Gm (15 gr) in 20 ml water by duodenal tube. Follow in 2 hours with a sodium or magnesium sulfate purge. Examine stools for the head of the worm. Crystoids Anthelmintic® as administered in ascariasis is the drug of choice for the treatment of light infections with *Hymenolepis nana* (dwarf tapeworm). For heavy infections use quinacrine hydrochloride as for treatment of *Taenia saginata* infections.

**B. General Measures.** Hospitalization is recommended for the treatment of persons with tapeworm infection. The success of treatment depends upon the cooperation of the patient, the physician, and the laboratory personnel. Proper pretreatment preparation of the patient and adequate postpurgation examination of stools for the head of the tapeworm are necessary. The stools should be examined after 6 months.

### Prognosis.

Because the prognosis is often poor in cerebral cysticercosis, the eradication of a *T. solium* infection is a matter of much greater urgency than that of the other tapeworm infections, which are usually benign. With careful treatment adult tapeworms can be eliminated safely and with minimal discomfort to the patient.

Tobling, W.H., & A.W. Woodruff. Treatment of tapeworm infections in man. *Brit. M. J.* 2 542-4, 1959.

## ECHINOCOCCOSIS (Hydatid Disease)

### Essentials of Diagnosis

- Cystic tumor of liver, lung, or, rarely, bone, brain, or other organs.
- Allergic manifestations, including urticaria, asthma, pruritus
- Eosinophilia (5-50%)
- History of close association with dogs in an endemic area.
- Positive complement fixation and skin tests

Hydatid cysts must be differentiated from abscesses, malignancies, tuberculosis, and syphilis. X-ray examination may be sufficient for diagnosis of pulmonary cysts but is less helpful for cysts in other sites. When both the Cassoni intracutaneous test and complement fixation are positive and there is an eosinophilia of more than 5%, the diagnosis is usually definite.

### General Considerations.

Human echinococcosis results from parasitism by the larval stage of the small tapeworm, *Echinococcus granulosus*. This tapeworm is found in various hosts throughout the world, but the areas of heaviest human infection are those where sheep are raised, notably Argentina, Uruguay, Greece, and other Mediterranean countries. In North America echinococcosis occurs sporadically, but it is a problem only in Alaska and northwestern Canada, where Indians and Eskimos are occasionally infected. The definitive host of the adult worm is usually the domestic dog, other canines, including wolves, foxes, and jackals are locally important hosts. The sheep is the common host for the larval worm, but cattle, hogs, and, in northwestern North America, caribou and moose may also be infected. Man acquires the infection by ingesting eggs transferred from hand to mouth. The source of eggs is usually the fur of infected dogs. Once swallowed, the eggs liberate embryos which invade the blood stream through the intestinal wall and are carried to the liver. Most larvae are trapped and encyst (as hydatid cysts) in the liver, some may reach the lung, where they develop into pulmonary hydatids, only rarely do larvae reach the brain, bones, skeletal muscles, kidneys, or spleen. Hydatid cysts are normally unilocular, occasional multilocular or alveolar cysts are thought to be the larval stages of another tapeworm species, *E. multilocularis*.

### Clinical Findings.

**A Symptoms and Signs** A liver cyst often remains silent for 5-10 years until it becomes large enough to be palpable or visible as an abdominal swelling. Such cysts rarely produce pressure effects, and cause no symptoms unless they begin to leak or are ruptured. When fluid and hydatid sand does escape from a cyst, pruritus, urticaria, asthma, and other allergic manifestations may appear and the eosinophil count rises. If the cyst ruptures suddenly, anaphylaxis and even sudden death may occur. Pulmonary cysts cause no symptoms (unless leaking occurs) until they become large enough to obstruct the bronchi, causing segmental collapse, or to erode into a bronchus and rupture. Cysts in the brain, symptomatic at a much earlier stage, may cause seizures or symptoms of increased intracranial pressure.

**B Laboratory Findings** When clinical findings, history and x-ray point to hydatid cyst, the diagnosis can be confirmed with the Casoni intracutaneous test, positive in about 85% of cases and the complement fixation test, positive in about 90% of cases. The eosinophil count is usually about 5-20% in asymptomatic cases, but it may go as high as 50% when allergic symptoms are present. Diagnosis may occasionally be made by examination of hydatid sand coughed up from a ruptured pulmonary cyst. Because of the danger of leakage or rupture, diagnostic aspiration of suspected hydatid cysts should never be undertaken. The final diagnosis is often made only by examination of cyst contents after surgical removal.

### Differential Diagnosis.

Hydatid cysts in any site may be mistaken for a variety of malignant and nonmalignant tumors or for abscesses, both bacterial and amebic. In the lung a cyst may be confused with an advanced tubercular lesion. Syphilis may also be confused with echinococcosis. Allergic symptoms arising from cyst leakage may resemble those associated with many other diseases.

### Complications

Sudden rupture of a cyst leading to anaphylaxis and sometimes death is the most important complication of echinococcosis. If the patient survives the rupture he still faces the danger of multiple secondary cyst infections arising from seeding of daughter cysts. Segmental lung collapse, secondary infections of cysts, secondary effects of increased intracranial pressure, and severe renal damage due to kidney cysts are other potential complications.

### Treatment.

The only definitive treatment is surgical removal of the intact cyst. Often, however, the presence of a cyst is only recognized when it begins to leak or when it ruptures. Such an event calls for vigorous treatment of allergic symptoms or emergency management of anaphylactic shock.

### Prognosis.

Patients may live for years with relatively large hydatid cysts before their condition is diagnosed. Liver and lung cysts often can be removed surgically without great difficulty, but for cysts in sites less accessible to surgery the prognosis is less favorable. The prognosis is always grave in secondary echinococcosis. About 15% of patients with echinococcosis may eventually die because of the disease or its complications.

Echinococcosis (editorial). *Ann.Int.Med.* 52: 464-76, 1960.

## NEMATODE (ROUNDWORM) INFECTIONS

### TRICHINOSIS

#### Essentials of Diagnosis

- Muscle pains and tenderness, fever, periorbital edema, and splinter hemorrhages
- Nausea, vomiting, cramps, and diarrhea
- History of ingestion of raw or improperly cooked pork
- Eosinophilia (as high as 75%)
- Positive skin test, muscle biopsy, and serologic tests

Early acute manifestations are primarily gastrointestinal and are readily confused with other acute intestinal disorders such as food poisoning. When many of the typical signs and symptoms appear, diagnosis usually causes no difficulty. Individual manifestations may lead to confusion with such diseases as dengue, rheumatic fever, myositis, poliomyelitis, brucellosis, and encephalitis.

## General Considerations

Trichinosis is an acute infection caused by the roundworm, *Trichinella spiralis*. Although cosmopolitan in distribution, for dietary reasons this parasite is a greater problem in many temperate areas than in the tropics. It is a common parasite of garbage-fed hogs in the United States, and autopsy figures suggest that 10-20% of the human population have been infected at one time or another. Man acquires the infection by eating encysted larvae in raw or undercooked pork, bear, or walrus. In the stomach and duodenum the larvae emerge and rapidly mature. Mating takes place and the female worms burrow into the small intestinal mucosa, producing gastrointestinal symptoms which may be mild or severe depending upon their numbers. The females discharge larvae which migrate in the blood stream to many parts of the body. Larvae reaching striated muscle encyst and remain viable for several years. Calcification of the cysts usually begins within a year. The larvae which do not reach muscle are eventually destroyed. Adult worms and larvae are only rarely found in the stool.

## Clinical Findings

**A Symptoms and Signs.** The clinical picture varies considerably in severity depending upon the number of larvae disseminated, the tissues invaded, and the general health of the patient, thus the acute disease may be mild or fatal. Gastrointestinal symptoms, if any usually occur within 2-3 days after eating infected pork. These irritative symptoms are followed a few days later by manifestations of larval migration and muscle invasion including fever, chills, muscle pains and tenderness, difficulty in swallowing and speaking, splinter hemorrhages, periorbital edema, edema of other dependent parts, urticaria, conjunctival and retinal hemorrhages, and photophobia. Still later, inflammatory reactions around larvae that have failed to reach striated muscle may produce meningitis, encephalitis, myocarditis, pneumonitis, and peripheral and cranial nerve disorders. If the patient survives, the fever usually subsides and recovery begins in the fourth week after onset of symptoms. Vague muscle pains and malaise may persist for several more months.

**B Laboratory Findings.** Eosinophilia appears in the second week after onset of symptoms, rises to a maximum of 20-75% in the third or fourth week, and then slowly declines to normal. A delayed reaction to the trichinella skin test (noted only after 12-24 hours) occurs early in the disease (fourth to

seventh days), while an immediate reaction to the test (noted after 5 minutes) usually occurs from the third week on. The skin test may remain positive up to 7 years after recovery. Precipitation and complement fixation tests become positive in the second or third week of the disease. The precipitation test may remain positive up to 2 years, the complement fixation test up to 9 months. Stool examinations rarely reveal either adult worms or larvae but encysted larvae may be demonstrated by muscle biopsy (deltoid, biceps, gastrocnemius) in the third to fourth weeks of the disease. Chest x-rays during the acute phase may show disseminated or localized infiltrates.

## Differential Diagnosis

Mild cases and those with atypical symptoms are often difficult to diagnose. Because of its protean manifestations, trichinosis may resemble many other diseases. (A list of at least 50 such diseases has been compiled.) Moderate to severe infections with some or all of the most typical signs and symptoms can however, usually be diagnosed readily. There are often several patients with similar symptomatology at the same time, and this is often the clue that leads to the diagnosis.

## Complications

Among the more important complications are secondary bacterial pneumonia, cerebral involvement, pulmonary embolism, and cardiac failure.

## Treatment.

Treatment is supportive and symptomatic. Severe acute cases require hospitalization and excellent nursing care. Corticotropin (ACTH) and the cortisones provide effective relief for the acute symptoms. A reduction of the eosinophil count, disappearance of fever and splinter hemorrhages, and a general improvement in the clinical state of the patient are guides which should be employed to determine the efficacy of treatment. In the acute stage, treat with relatively large doses of either drug for the first 24-48 hours. In the subacute stage therapy may have to be continued for several days or weeks to prevent recurrence. Give in reduced dosage sufficient to keep symptoms under control.

## Prognosis

The mortality rate for clinical trichinosis in the United States is probably about 5%. Death may occur in 2-3 weeks in overwhelming infections, more often it occurs in 4-8 weeks from a major complication such as cardiac failure or pneumonia.

Kagan, I. G.: Trichinosis in the United States.  
 Pub. Health Rep. 74:159-62, 19

### TRICHURIASIS (Trichocephaliasis)

#### Essentials of Diagnosis

- Most infections are silent, heavy infections may cause abdominal pain, distention, flatulence and diarrhea
- Characteristic barrel-shaped eggs in the stool

Symptomatic trichuriasis is not clinically distinctive. Diagnosis depends upon demonstration of the characteristic eggs in stool specimens

#### General Considerations

*Trichuris trichiura* is a common intestinal parasite of man throughout the world, particularly in the subtropics and tropics. The small slender worms, often called whipworms, attach themselves to the mucosa of the large intestine, particularly the cecum. The worms cause symptoms only when present in very large numbers. Eggs passed in the feces require 2-4 weeks for larval development after reaching the soil before becoming infective. New infections are acquired by direct ingestion of infective eggs.

#### Clinical Findings

**A. Symptoms and Signs** Light to moderate infections rarely cause symptoms. Heavy to massive infections may be accompanied by a variety of symptoms arising from irritation of the mucosa. Among the most common of these are abdominal pain, tenesmus, diarrhea, distention, flatulence, nausea, vomiting, and weight loss. Heavy infections are most often found in malnourished young children. Dowel perforation with peritonitis and rectal prolapse may occur.

**B. Laboratory Findings** Detection of whipworm eggs in the stool is usually essential for diagnosis. Eosinophilia (5-20%) is common with all but light infections, and hypochromic anemia has been attributed to heavy infection when there is erosion and sloughing of the mucosa.

#### Treatment

Asymptomatic light infections may be left untreated. For other infections treat with dithiazanine iodide (Abminthic<sup>®</sup>, Delvez<sup>®</sup>), 100

mg t.i.d. the first day and 200 mg. t.i.d. for 4 additional days for adults and children over 60 lb. The drug should be taken after meals. For children under 60 lb. use a total of 50 mg/10 lb. body weight in divided doses on the first day and 100 mg/10 lb. body weight in divided doses for 4 additional days. If necessary a second course may be given after 1-2 weeks. Continue treatment with reduced dosage if nausea or diarrhea occurs. Discontinue treatment or interrupt treatment for a few days if severe vomiting is provoked. No other drug appears to be as effective as dithiazanine. If it is not available hexylresorcinol may be used as for ascariasis (see below).

Paine, D. H. D., & others: Treatment of trichuriasis with dithiazanine in a hospital for mental defectives, Brit. M. J. 1:770-4, 1950.

### ASCARIASIS

#### Essentials of Diagnosis

- Pneumonitis with fever, cough, hemoptysis, urticaria, and accompanying eosinophilia
- Vague abdominal discomfort and colic
- Inflammatory reactions in organs and tissues invaded by wandering adult worms
- Characteristic ovs in the stool, larvae in the sputum

Ascariasis must be differentiated from allergic disorders such as urticaria, Löffler's syndrome, and asthma. The pneumonitis associated with ascariasis is similar to other types of pneumonitis, especially that occurring with hookworm or *Strongyloides* infection. Ascaris-induced pancreatitis, appendicitis, diverticulitis, etc., must be differentiated from other causes of inflammation of these tissues.

#### General Considerations

*Ascaris lumbricoides*, a large intestinal roundworm, is the most common of the intestinal helminths of man. It is cosmopolitan in distribution, although it flourishes best in warm, humid climates. In temperate regions it is generally associated with low standards of personal hygiene. The adult worms live in the small intestine. After fertilization, the female produces enormous numbers of characteristic eggs which are carried out to the soil in feces.



Under suitable conditions the eggs become infective, containing an active larva, in 2-3 weeks. Man is infected by ingestion of the mature eggs in fecally contaminated food and drink. The eggs hatch in the small intestine, releasing motile larvae which penetrate the wall of the small intestine and reach the right heart via the mesenteric venules and lymphatics. From the heart they move to the lung, burrow through the alveolar walls, and migrate up the bronchial tree into the pharynx, down the esophagus, and back to the small intestine. The larvae mature and female egg production begins about 60-75 days after ingestion of the infective eggs. The large adult worms, 20-40 cm long, may live for a year or more.

### Clinical Findings

**A Symptoms and Signs** No symptoms arise from the early migration of the larvae after hatching. In the lung, however, they damage capillary and alveolar walls as they force their way through. Considerable hemorrhage may result from this trauma and accumulations of leukocytes and serous exudates in and around the airspaces may lead to consolidation. Pneumonitis occasionally develops with heavy infections. Symptoms and signs include fever, cough, hemoptysis rales, and other evidences of lobular involvement. Eosinophilia is usual at this stage, and urticaria is not uncommon. After passage through the lungs it is believed that the larvae may go astray, lodging in the brain, kidney, eye, spinal cord, or skin. Many bizarre symptoms may result from such invasions.

Small numbers of adult worms in the intestine usually produce no symptoms. With heavy infection vague abdominal discomfort and colic may occur, particularly in children. Intact worms are occasionally passed. Mild allergic manifestations, particularly urticaria and eosinophilia, may persist during the intestinal phase. When the infection is heavy and particularly if the worms are aroused by dietary indiscretion or certain oral medications, wandering may occur. Adult worms may be coughed up, vomited, or passed out through the nose. They may also force themselves into the common bile duct, the pancreatic duct, the appendix, diverticula, and other sites. Mechanical blockage and inflammation usually result. With very heavy infestations masses of worms may cause intestinal obstruction and even bowel perforation. It is important that *Ascariis* infections be cured prior to bowel surgery because the worms have been known to break open suture lines postoperatively.

**B Laboratory Findings** The diagnosis usually depends upon finding the characteristic eggs in stool specimens. Occasionally a spontaneously passed adult worm reveals a previously unsuspected infection. There are no characteristic alterations of the blood picture during the intestinal phase. Skin tests are of no value in diagnosis. During the pulmonary phase there may be eosinophilia, and larvae may occasionally be found in the sputum.

### Complications & Sequelae.

Bacterial pneumonia may be superimposed upon pneumonitis resulting from larval migration. During the migratory stage allergic manifestations may be severe.

### Treatment

**A Piperazine** Many brands of syrups and tablets of piperazine citrate or phosphate are available. Usually each ml of syrup contains the equivalent of 100 mg piperazine hexahydrate, tablets usually contain 250 or 500 mg. The following daily doses may be given at any time and without special diet or purgation. If necessary, repeat after one week.

Up to 30 lb	- 1 Gm	} Once daily for 2 consecutive days
30 to 50 lb	- 2 Gm	
50 to 100 lb	- 3 Gm	
Over 100 lb	- 3.5 Gm	

**B Hexylresorcinol** Give 30 Gm (1 oz) magnesium sulfate in water, or 240 ml (8 oz) of solution of magnesium citrate the night before drug therapy. A light meal is given on the preceding evening and then no food until at least 5 hours after taking the hexylresorcinol. Alcohol is contraindicated before and during treatment. Hexylresorcinol, 5 hard gelatin capsules, 0.2 Gm (3 gr) (crystoids) (total 1 Gm) is given in the morning on an empty stomach. These are to be swallowed whole, not chewed. Doses for children: Under 6 years of age, 0.4 Gm (6 gr); 6-8 years, 0.6 Gm (9 gr); 8-12 years, 0.8 Gm (12 gr). Two hours later give 30 Gm (1 oz) magnesium sulfate in water to remove the worms from the bowel. Repeat 2 hours later, if necessary, for purgation. Stool examination should be made one week later on 3 successive days to determine efficacy of treatment. Treatment may be repeated in 3 days if necessary.

**C Diethylcarbamazine citrate (Hetrazan®)** Give 3-6 mg /Kg body weight orally 3 times daily for 7-11 days. A syrup preparation containing Hetrazan® powder in a concentration of 30 mg /ml is recommended for small children. Administer 12 mg /Kg body weight once a day.

for 4 days or 6-10 mg /Kg body weight t i d for 7-10 days When Hetrazan<sup>®</sup> is used for eradication of *Ascaris lumbricoides* pretreatment fasting and post-treatment purgation are not necessary

**D Oil of Chenopodium and Tetrachloroethylene** May be used if other preparations are ineffective or not available (Caution Tetrachloroethylene stimulates activity of *Ascaris* and may result in bowel obstruction ) Follow procedure of treatment as mentioned above for hexylresorcinol Oil of chenopodium 0.3 ml (4½ min ) capsule, and tetrachloroethylene 3 soluble gelatin capsules 1 ml (15 min ) (total dose 3 ml ) are given together and followed by purgation as above

### Prognosis

A heavy infection is usually not dangerous as long as the adult worms stay in their normal habitat but the long list of major complications caused by wandering adults plus the possibility of intestinal obstruction requires that such infections be treated as soon as they are recognized

Bumalo, T.S. & L.J. Plummer Piperazine (antepar) in the treatment of pinworm and roundworm infections M Clin North America 41 575-85, 1957

## STRONGYLOIDIASIS

### Essentials of Diagnosis

- Pruritic dermatitis at sites of penetration of larvae
- Malaise, cough urticaria
- Colicky abdominal pain, flatulence, diarrhea alternating with constipation
- Eosinophilia, characteristic larvae in fresh stool specimens

Initial dermatitis may resemble hookworm ground itch or the creeping eruption associated with *Ancylostoma braziliense* infection The gastrointestinal symptoms must be distinguished from similar gastrointestinal disorders due to other causes

### General Considerations

Strongyloidiasis is caused by the roundworm, *Strongyloides stercoralis* It is common in tropical and subtropical areas throughout the world In the United States it is prevalent in the southeastern states The adult female worm burrows into the mucosa

of the intestinal villi and lays eggs within the tissues The duodenum and jejunum are most heavily infected The eggs develop into rhabditiform larvae which are passed in the feces The free-living rhabditiform larvae then develop into infective filariform larvae These larvae penetrate the skin of the next victim enter the blood stream, and are carried to the lungs where they escape from capillaries into alveoli and ascend the bronchial tree to the glottis The larvae are then swallowed and carried to the small intestine, where maturation to the adult stage takes place The time from skin penetration to egg laying by the mature adult is about 4 weeks The life span of the adult worm may be as much as 5 years

Auto-infection may occur if the rhabditiform larvae are retained in constipated feces or if there is fecal contamination of the perianal region Such infection may also occur in the presence of diarrhea Auto infection is responsible for the persistence of strongyloidiasis in persons who have left endemic areas

### Clinical Findings

**A Symptoms and Signs** The clinical picture is not distinctive, diagnosis depends upon laboratory demonstration of larvae in the feces At the points of entry of larvae into the skin there may be erythema and a fine papular, intensely pruritic eruption Papules may develop into vesicles coalesce and discharge serous fluid or they may become hemorrhagic Malaise and fever may occur with the dermatitis in severe cases Vague signs and symptoms during the migratory stage may include malaise, anorexia, fever, and cough Urticaria is not uncommon Secondary bacterial pneumonia may be initiated by a heavy larval migration through the lungs An asymptomatic period of a few weeks usually precedes the gastrointestinal symptoms of which the most common is localized or diffuse colicky abdominal pain Diarrhea is common, often alternating with constipation or periods of normal bowel activity With heavy infection, diarrhea may be persistent and accompanied by lassitude, nausea, vomiting, flatulence, weight loss, and debilitation

**B Laboratory Findings** During the stage of larval migration there is eosinophilia of 10-50% as well as leukocytosis up to 20,000/cu mm In the intestinal phase eosinophilia may range from normal to 10% but the WBC is usually normal except in severe acute infections A mild anemia may be present in this phase The diagnosis is based on finding the characteristic rhabditiform larvae in a fresh stool specimen Eggs are rarely found

in the stool even in the case of severe diarrhea. Duodenal intubation may be required to establish the diagnosis when larvae are not found in the stools. Duodenal contents are examined directly or after concentration. Larvae are occasionally found in the sputum or urine. Fecal cultivation may produce larvae or free living adults after about 48 hours. Serologic and intradermal tests are not of diagnostic value.

### Differential Diagnosis

Because of the varied signs and symptoms at different stages of the infection, diagnosis may be difficult. During the stage of skin invasion, hookworm ground itch and creeping eruption due to *Ancylostoma braziliense* are the conditions which most closely resemble *Strongyloides* ground itch, particularly because of the ankle-foot distribution of the skin lesions. During the later stages of the infection, many causes of transient pneumonitis, urticaria, and gastrointestinal symptoms may have to be considered. Sputum and stool examinations for parasites will help to rule out other helminthic infections (suggested by the presence of eosinophilia).

### Complications

Larval migration through the lungs may initiate a secondary bacterial pneumonia. Hepatitis, cholecystitis, myocarditis, paralytic ileus, and meningitis may occur with massive infections. Associated hookworm or *Ascariis* infection is not uncommon.

### Treatment

Treat with dithiazanine iodide (Abmintic® Deltex®) 200 mg daily for patients of up to 30 lb body weight and 100 mg for each additional 10 lb body weight to a maximum for adults of 600 mg/day. Give in divided doses 2 or 3 times daily for 10-14 days. Interrupt treatment for a few days if severe vomiting is provoked or change to gentian violet or pyriminyl chloride (Vanquin®). The dosage of gentian violet for adults and older children is 65 mg (1 gr) one hour before meals t i d until 3-3 Gm (50 gr) have been given for younger children give 10 mg ( $\frac{1}{8}$  gr) daily in divided doses t i d for each year of apparent (not chronologic) age to the maximum adult dose. Gentian violet is far less effective than dithiazanine. With any of these drugs, reduce dosage by one third or interrupt treatment if there is epigastric pain or severe vomiting (or with gentian violet, violet discoloration of urine).

In the case of co-infection with *Ascaris* or hookworm, which is not uncommon, treat the co-infection first and the strongyloidiasis afterward.

### Prognosis

Favorable except in massive infections usually resulting from auto-infection, which may result in intractable diarrhea, severe debilitation, and complications as noted above.

Huchton, P., & R. Horn. Strongyloidiasis. *J Pediatr* 55:602-8, 1959.

## ENTEROBIASIS (Pinworm Infection)

### Essentials of Diagnosis

- Perianal pruritus, usually nocturnal, associated with insomnia and restlessness.
- Vague gastrointestinal symptoms.
- Adult worms in stool, eggs on skin of perianal area.

Pinworm pruritus must be distinguished from similar perianal pruritus due to various mycotic infections, allergies, and psychologic disorders. Gastrointestinal complaints may be confused with those resulting from infections with other intestinal helminths or from a great variety of other causes.

### General Considerations

*Enterobius vermicularis*, a short spindle-shaped roundworm often called the pinworm, is world-wide in distribution and the most common cause of helminthic infection of man in the United States. Man is the only host for the parasite. Children are more often affected than adults. The adult worms inhabit the cecum and adjacent bowel areas, lying with their heads loosely attached to the mucosa. When the fertilized female worms become gravid, they migrate down the colon and out onto the skin, where eggs are deposited in large numbers. The females die after oviposition. The eggs become infective in a few hours and may then infect man if transferred to the mouth by inhalation or more commonly by hand food or drink contamination. The eggs are resistant to household disinfectants and drying and may remain infective in dust for a considerable time. Retroinfection occasionally occurs when the eggs hatch on the perianal skin and the larvae migrate through the anus into the large intestine. If infective eggs are swallowed, they hatch in the duodenum and the larvae migrate down to the cecum, moulting twice en route. The development of a mature ovipositing female from an ingested egg requires about 2 months.

**Clinical Findings.**

**A Symptoms and Signs** The most common and most important symptom is pruritus of the perianal area particularly at night. Insomnia, restlessness, enuresis and irritability are common symptoms particularly in children. Many mild gastrointestinal symptoms - abdominal pain, nausea, vomiting, diarrhea, anorexia - have also been attributed to enterobiasis although the association is difficult to prove. It is claimed that these symptoms result from mucosal irritation by the adult worms in the cecum, appendix and surrounding portions of the bowel.

**B Laboratory Findings** Except for a modest eosinophilia (4-12%) the blood picture is usually normal. The diagnosis depends upon finding adult worms in the stool or eggs on the perianal skin. Eggs are seldom found on stool examination. The most reliable diagnostic technique consists of applying a short strip of pressure-sensitive cellulose tape to the perianal skin and spreading it on a slide for study. Three such preparations made on consecutive mornings before bathing or defecation will establish the diagnosis in about 90% of cases. Five to 7 such examinations are necessary before the diagnosis can be ruled out.

**Complications**

It has been postulated that the presence of large numbers of worms in the cecum may predispose to appendicitis but the evidence for this is inconclusive. Female worms occasionally migrate into the vagina, uterus and fallopian tubes where they may encyst.

**Treatment.**

**A General Measures** Treat all infected members of the family and other groups of close contacts since reinfection from non-treated contacts is frequent. Hygienic instruction is of particular importance, e.g. careful washing of hands with soap and water after defecation and again before meals. Fingernails should be kept trimmed close and clean, and the patient should abstain from scratching involved areas and should not put his fingers in his mouth. Carbolyated petrolatum should be applied to the anal region after defecation, and the anal region should be washed thoroughly in the morning with soap and water. Toilet seats should be scrubbed with soap and water daily, and bed linens boiled twice a week. Pajamas (or "sleepers" for children) should be worn to prevent manual contact with anal region during sleep. Raise the temperature of the bedroom as high as possible for one hour every day and then air thoroughly.

**B Specific Measures** (in order of effectiveness)

1 Piperazine - Available in syrup containing 100 mg./ml. or as tablets of 250 or 500 mg. The dosage is as follows:

Up to 15 lb	- 250 mg daily
15 to 30 lb	- 250 mg b i d
30 to 60 lb	- 500 mg b i d
Over 60 lb	- 1 Gm b i d

2 Pyrvinium pamoate in syrup, single dose of 5 mg./Kg. body weight, warrants further trial and may become the drug of choice.

3 Dithiazanine iodide (Abminthic<sup>®</sup>, Delvex<sup>®</sup>) For patients weighing over 60 lb., give 100 mg. t i d on the first day and 100-200 mg. t i d for 4 days thereafter, for patients weighing less than 60 lb., give half those amounts. Reduce dosage or interrupt treatment if severe vomiting occurs.

4 Methylrosaniline chloride (four-hour enteric-coated tablets), 1 mg. (1/60 gr.)/lb. body weight in 3 divided doses daily before meals. Give for 8-10 days and repeat course after an interval of one week.

**Prognosis**

Although annoying, the infection is benign. Cure is readily attainable with one of several effective drugs but reinfection is a major problem in many households. Thus the general measures cited above are of great importance.

Bumbalo, T. S., & others. A clinical evaluation of four oxyuricides. *Am J Dis Child* 99:617-21, 1960.

**✓HOOKWORM DISEASE****Essentials of Diagnosis**

- Weakness, fatigue, pallor, palpitation, dyspnea associated with a hypochromic microcytic anemia.
- Diarrhea, flatulence, abdominal discomfort, weight loss.
- Transient episodes of coughing with sore throat and bloody sputum.
- Pruritic, erythematous, maculopapular or vesicular dermatitis.
- Characteristic eggs in the stool, guaiac-positive stool.

The initial dermatitis or ground itch resembles that of strongyloidiasis. Creeping eruption caused by nonhuman hookworm species may resemble ground itch. Pulmonary symptoms are similar to but less severe than those associated with larval migration in ascariasis and strongyloidiasis. The later manifestations of hookworm infection cannot be attributed to this parasite on clinical grounds alone; final diagnosis depends upon finding eggs in the stool.

### General Considerations

Hookworm disease, widespread in the tropics and subtropics, is caused by *Ancylostoma duodenale* and *Necator americanus*. In the Western Hemisphere *Necator* is the prevailing genus. The adult worms, approximately 1 cm (3/8 inch) long, attach themselves to the mucosa of the small intestine, where they suck blood and mucosal substances. Symptomatology and pathology are proportionate to the number of worms infecting the patient. A burden of at least 100 worms is necessary to produce anemia and symptoms in an adult. Eggs produced by the female worms are passed in the stool, which must fall on warm, moist soil if larval development is to take place. Infective larvae remain in the soil until they come in contact with human skin. After penetrating the skin the larvae migrate through the lungs and eventually reach the small intestine where final development into adult worms takes place.

### Clinical Findings

**A. Symptoms and Signs** Ground itch, the first manifestation of hookworm infection, is a pruritic erythematous dermatitis, either maculopapular or vesicular, associated with the invasion of infective larvae. The severity of the dermatitis is a function of the number of invading larvae and the sensitivity of the host. The pulmonary phase of the disease is a transient reaction to larval migration through the lungs. Bloody sputum and cough result from damage caused by larvae breaking into alveoli from small blood vessels. Two or more weeks after the skin invasion, and depending upon the number of worms present, abdominal discomfort, flatulence, diarrhea, and other symptoms of intestinal irritation may appear as worms begin to attach themselves to the mucosa. Anemia appears 10-20 weeks after infection. The severity of the anemia depends upon the worm burden: more than 500 worms are necessary to produce profound anemia. The pa-

tient's nutritional status will also influence the severity of the anemia.

**B. Laboratory Findings** Final diagnosis depends on demonstration of characteristic eggs in the stool. Occasionally larvae may be discovered in either the stool or sputum. The stool contains occult blood. The severity of the hypochromic microcytic anemia will depend upon the worm burden, which can be estimated by egg counting techniques. Eosinophilia is usually present, particularly in the early months of the infection.

### Complications

The skin lesions may become secondarily infected. In highly sensitive individuals the allergic reaction to the invading and migrating larvae may be so severe as to require treatment. With profound anemia there may be cardiac decompensation with edema and ascites, mental retardation, stunting of growth, and impaired renal function.

### Treatment

**A. General Measures** Estimation of the need for treatment should be based upon quantitative counts of the eggs in the stools. Light infections require no treatment, particularly if it occurs after treatment of heavy infection. It is often impossible to completely eradicate the infection.

Provide an adequate high-protein diet with supplementary iron medication. Rule out the possibility of coincidental ascariasis. If ascariasis is present, or when diagnostic facilities are limited, give preliminary hexylresorcinol as prescribed for ascariasis (see p. 703). Tetrachloroethylene stimulates ascariasis activity which occasionally results in intestinal obstruction. If large numbers of hookworms are still present following the administration of hexylresorcinol, wait one week following the last dose and give tetrachloroethylene.

### B. Specific Measures

**1. Tetrachloroethylene** is the drug of choice. Caution. Be sure to correct malnutrition and anemia before giving this drug. Tetrachloroethylene is contraindicated in patients with alcoholism, chronic gastrointestinal disorders, severe constipation, hepatic disease, and in patients undergoing heavy metal therapy.

Give 30 Gm (1 oz) magnesium sulfate in water or 240 ml (8 oz) magnesium citrate solution the night before drug therapy. Elim-

inate alcohol and fatty foods for 48 hours before medication, give a light evening meal, and give no more food until after medication and the subsequent purge. Tetrachloroethylene, 3-5 soluble gelatin capsules containing 1 ml (15 min.), should be given in the morning on an empty stomach. Saline purgation, 2-3 hours later, is essential. Examine stools one week later on 3 successive days to determine efficacy of treatment. Repeat treatment in 2 weeks if stools are positive. Ferrous sulfate, 0.2-0.3 Gm (3-5 gr) t.i.d. after meals, is usually indicated for anemia.

2. Hexylresorcinol may be used if tetrachloroethylene is contraindicated, ineffective, or not available.

3. Bephenium hydroxynaphthoate (Alcopar<sup>®</sup>) is a new, apparently nontoxic compound which may become a useful alternative to tetrachloroethylene. Although its optimum dose has not yet been determined, it is probably close to 5 Gm given as a single dose with 40 ml of water regardless of the age of the patient.

### Prognosis

If the disease is recognized before serious secondary complications appear, the prognosis is favorable. With iron therapy, improved nutrition and administration of an anthelmintic, complete recovery is the rule. The persistence of a few eggs in the stool of an asymptomatic person who is not anemic is not an indication for repeated treatments.

Mackerras, M.J. A promising new drug for the elimination of hookworms. *M.J. Australia* 12:261-3, 1961.

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## VISCERAL LARVA MIGRANS

Infection by the larval dog and cat ascarids *Toxocara canis* and *T. cati*, usually occurs in young children as a result of dirt eating. The larvae, unable to mature in an abnormal host, migrate through the body and lodge in various organs, particularly the lungs, liver, and brain. Because the disease is difficult to diagnose its distribution is not well known, but it is probably cosmopolitan.

Fever, cough, hepatomegaly, and nervous symptoms are the commonest clinical findings. A variety of other symptoms may occur when such organs as the heart, eyes, and kidneys

are invaded. Many infections are asymptomatic. Eosinophil counts of 30-80% and leukocytosis are common. Hyperglobulinemia occurs when the liver is extensively invaded.

There is no specific treatment. The cortisones, antibiotics, antihistamines, and analgesics may be needed to provide symptomatic relief. Symptoms may persist for months, but the ultimate prognosis is usually good.

Heiner, D.C., & S.V. Kevy. Visceral larva migrans: report of the syndrome in three siblings. *New England J. Med.* 254:629-35, 1956.

## FILARIASIS

### Essentials of Diagnosis

- Recurrent attacks at irregular intervals of lymphangitis, lymphadenitis, fever, orchitis
- Hydrocele, chyluria, elephantiasis of legs, arms, genitalia, or breasts
- Characteristic microfilariae in the blood
- Eosinophilia, positive skin or complement fixation tests

Hydrocele and elephantoid tissue changes in persons residing in endemic areas are usually filarial in origin. Definitive diagnosis depends upon demonstration of adult worms or microfilariae, or positive skin tests or complement fixation tests. Elephantiasis in those who have visited endemic areas only briefly is rarely due to filariasis. Many infections are asymptomatic and detected only by blood examination. Diagnosis of early cases is often difficult because attacks of lymphangitis, adenitis, and fever are transitory and microfilariae may be rare in the blood.

### General Considerations.

Filariasis is caused by infection with one of 2 filarial nematodes, *Wuchereria bancrofti* and *Brugia malayi*. Infective larvae of *B. malayi* are transmitted to man by the bite of certain *Mansonia* and *Anopheles* mosquitoes of south India, Ceylon, south China, and southeast Asia. *W. bancrofti*, widely distributed in the tropics and subtropics of both hemispheres, is transmitted by certain *Culex* and *Aedes* mosquitoes. Over a period of months, adult worms

of both species mature in or near the superficial and deep lymphatics and lymph nodes. The adults produce large numbers of motile larvae (microfilariae), which appear in the peripheral blood. Microfilariae of *W. bancrofti* are found in the blood chiefly at night (nocturnal periodicity), except for a nonperiodic variety in the South Pacific. *B. malayi* microfilariae are usually nocturnally periodic but may be semi-periodic (present at all times with a slight nocturnal rise). While man is the only vertebrate host for *W. bancrofti*, cats, monkeys, and other animals may harbor *B. malayi*. Several other species of filarial worms infect man without causing important signs or symptoms. The microfilariae of 2 of these, *Dipetalonema perstans* (African and South American tropics) and *Mansonella ozzardi* (West Indies and South America), appear in the blood and must be differentiated from those of the pathogenic species.

### Clinical Findings.

**A. Symptoms and Signs.** The early clinical manifestations are inflammatory, those of the later stages are obstructive. Episodes of fever, with or without inflammation of lymphatics and nodes, occur at irregular intervals in typical early cases. Persistent lymph node enlargement is most common in *B. malayi* infections but occurs in some *W. bancrofti* endemic areas. Funiculitis and orchitis are common and abscesses may form at sites of lymphatic inflammation. Such episodes may occur intermittently for months or years before the first obstructive signs appear. The number and severity of these attacks, and the extent of the later changes, depends primarily upon the intensity of the infection, which in turn is related to the length of residence in an endemic area. Obstructive phenomena, arising from interference with normal lymphatic flow, include hydrocele, scrotal lymphedema, lymphatic varices, and elephantiasis. Chyluria may result from rupture of distended lymphatics into the urinary tract. In the early stages of elephantiasis the tissues of the affected part are edematous and soft, later, with skin hypertrophy and subcutaneous connective tissue proliferation, the part becomes hard. As the swelling enlarges, sometimes to enormous size, the skin surface folds and fissures. Bancroftian elephantiasis frequently involves the legs and genitalia, less often the arms and breasts, in *B. malayi* infections elephantiasis of the legs below the knees is most common and genital structures are rarely affected

**B. Laboratory Findings** Eosinophilia (10-30%, higher with *B. malayi*) is usual in the early stages, the count falls, sometimes to normal, as elephantiasis develops. Microfilariae are rare in the blood in the first 2-3 years after infection, abundant as the disease progresses, and again rare in the advanced obstructive stage. Laboratory diagnosis usually requires demonstration of microfilariae, which must be differentiated from the non-pathogenic species. Both day and night blood specimens should be examined. Diagnosis can also be made by finding adult worms in biopsy specimens, but these should be taken only from lymphatics of the extremities. Removal of nodes may further impair drainage from the affected area. When microfilariae cannot be found, skin and complement fixation tests are fairly satisfactory for diagnosis. Skin tests are the more reliable (only 10% false-positive).

### Differential Diagnosis.

Diagnosis of the early febrile and inflammatory episodes may be difficult, particularly when the patient has moved away from an endemic area. Filarial funiculitis, orchitis, and epididymitis may suggest gonococcal infection, but there is no urethral discharge in the uncomplicated case. Among the late manifestations, elephantiasis may be confused with hernia, Milroy's disease, multiple lipomatosis, severe congestive heart failure, venous thrombosis, and obstructive lesions of the lymphatics, which may produce nonfilarial elephantiasis of the extremities. The last 3 named can be distinguished readily from filariasis. Multiple lipomas may produce a massive soft lumpy swelling of the proximal part of a limb. In contrast, the filarial lesion starts distally and becomes hard as it enlarges. Milroy's congenital elephantiasis usually involves both legs below the knees. The skin is smooth, there is no eosinophilia, and the patient often has never visited the tropics.

### Treatment.

**A. General Measures** Bed rest is indicated during febrile and local inflammatory episodes. Antibiotics should be given for secondary infections, particularly abscesses over inflamed nodes. Suspensory bandaging is a valuable palliative measure for orchitis, epididymitis, and scrotal lymphedema. Treat mild edema of a limb with rest, elevation, and firm bandaging. Chyluria usually requires no treatment except rest.

**B Surgical Measures** Surgical removal of the elephantoid scrotum, vulva, or breast is relatively easy and the results are usually satisfactory. Surgery for limb elephantiasis is difficult and the results are often disappointing. Attempt operation only if the swollen limb severely limits the ability of the patient to earn a living.

**C Specific Measures** Diethylcarbamazine (Hetrazan<sup>®</sup>) is the drug of choice. The usual dosage is 3 mg /Kg body weight orally t i d for 21 days. Use a single dose on the first day and regulate subsequent dosage to minimize allergic reactions common early in treatment as microfilariae are killed. The drug itself is nontoxic in usual doses. Microfilariae are rapidly destroyed but the drug has only a limited action on the adult worms. Since microfilarial relapses often occur 3-12 months after treatment, control of the infection may require several courses over 1-2 years. The principal value of the drug is in eliminating the patient as a source of infection. Drug treatment will not significantly influence the course of advanced filariasis.

### Prognosis

In early and mild cases the prognosis is good if the patient leaves the endemic area or if transmission in the area is reduced by control measures (mosquito control and drug treatment of human infections). Surgical treatment of genital elephantiasis often produces satisfactory results. For severe elephantiasis of a limb the prognosis is less favorable.

Raghaven N G S & others. Filariasis: Epidemiology-pathogenesis, chemotherapy vector-control. Bull World Health Organ 16 553-64, 1957.

Wilson T. Filariasis in Malays - a general review. Trans. Roy Soc Trop Med & Hyg 55 107-29, 1961.

## LOIASIS

Loiasis is a common and distinctive disease of tropical Africa caused by the filarial nematode, *Loa loa*. The intermediate host, *Chrysops* a biting fly, carries the infection from man or monkey to man. Infective larvae, introduced by the biting fly, develop into adult worms in about 12 months. It is the adult worms migrating through subcutaneous tissues

which cause the symptoms of loiasis, not the larval microfilariae in the bloodstream.

Many infected persons remain symptom free, others develop severe allergic reactions to the infection and sometimes emotional disturbances. The first definite sign of the disease is the appearance of a Calabar swelling or the migration of a worm across the eye. The swelling is a temporary, usually painless subcutaneous edematous reaction often several inches in diameter. The overlying and surrounding skin is often reddened, irritated and pruritic. The swelling may migrate a few inches before disappearing, more often it remains in one place for several days and then subsides. The reaction occurs most frequently on the hands, forearms, and around the eyes but it may appear anywhere. Some patients experience Calabar swellings at infrequent intervals others as often as twice a week. Migration of the worm across the eye produces a foreign body sensation often with considerable irritation. Migrating worms are sometimes visible in subcutaneous tissues elsewhere in the body. Generalized urticaria, edema of a whole limb, extensive erythema, and generalized pruritus have been reported in some patients.

The adult worm may be recovered from the eye or skin (rarely) or microfilariae may be found in daytime blood films (20-30% of patients). Complement fixation and skin tests are often useful in diagnosis. The eosinophil count is elevated, varying between 10-40% or more.

Surgical removal of adult worms is sometimes possible but the most satisfactory treatment is with diethylcarbamazine (Hetrazan<sup>®</sup>) a relatively nontoxic drug. Optimal dosage is 3 mg /Kg body weight t i d after meals for 21 days. Because allergic reactions (fever, urticaria, rashes, pruritus) are common early in treatment (probably as a result of rapid killing of microfilariae) use only a single dose on the first day of treatment and regulate subsequent dosage according to the patient's reaction. Antihistamine therapy is often helpful early in the course of treatment.

The prognosis is good with treatment. Without treatment, loiasis is annoying and uncomfortable but rarely life-endangering. Fatal encephalitis rarely occurs.

Gordon, R M., & others. The problem of loiasis in West Africa. Trans. Roy Soc Trop Med. & Hyg 44 11-41, 1950.



# CUTANEOUS LARVA MIGRANS (Creeping Eruption)

Creeping eruption, prevalent throughout the tropics and subtropics, is caused by the larvae of the dog and cat hookworms, *Ancylostoma braziliense* and *A. caninum*. It is a common infection of man in the southeastern United States, particularly where people come in contact with moist sandy soil (beaches, children's sand piles) contaminated by dog or cat feces. The larvae may invade any skin surface, but the hands or feet are usually affected. The larvae may remain active in the skin for several weeks or months, slowly advancing but rarely moving more than a few inches from the penetration site. Eventually, if not killed by treatment, the larvae die and are absorbed.

Soon after invasion of the skin, minute itchy erythematous papules appear at the site of entry. Two or 3 days later characteristic serpiginous eruptions begin to form as larval migration starts. These intensely pruritic lesions may persist for several months as migration continues. The parasite usually lies slightly ahead of the advancing end of the eruption. Vesiculation and crusting commonly occur in the later stages. About 30% of patients develop transient pulmonary infiltrates and eosinophilia, possibly representing larval migration through the lungs. There are no consistent laboratory findings in most cases.

The early stages may be confused with hookworm ground itch, *Schistosoma dermatitis*, skin reactions to larval *Strongyloides*, and reactions to various larval fly infestations. After serpiginous lesions develop there should be little difficulty in diagnosis.

Simple transient cases usually do not require treatment. The larvae must be killed to provide relief in severe or persistent cases. Freezing ahead of the eruption with ethyl chloride spray or CO<sub>2</sub> snow is often effective. Other methods include local injections of chloroquine or quinine (Atabrine®) and application of ethyl acetate collodion to the skin over the larvae. Systemic treatment with diethylcarbamazine (Hetrazan®) in doses of 2-4 mg./Kg body weight provides relief but is not curative. Antihistamines are helpful in controlling pruritus, and antibiotic ointments may be necessary to treat secondary infections.

When treatment is unsuccessful, symptoms may persist for several months. Barring reinfection, however, eventual recovery is certain.

Wright, D., & E. Gold. Löffler's syndrome associated with creeping eruption (cutaneous helminthiasis): report of 26 cases. Arch. Int. Med. 78:303-12, 1946.

# DRACONTIASIS (Guinea Worm Infection, Dracunculosis)

*Dracunculus medinensis* is a nematode parasite of man found through northern and central Africa, southern Asia, and northeastern South America. It occurs in the Caribbean but is not seen in the United States except in imported cases. Man is infected by swallowing water containing the infected intermediate host, the crustacean Cyclops, which is common in wells and ponds in the tropics. Larvae escape from the crustacean in the human host and mature in the connective tissues. After mating the male worm dies and the gravid female, now 1 meter (40 inches) or more in length, moves to the surface of the body. The head of the worm reaches the skin surface, a blister develops and ruptures, and the uterus discharges great numbers of larvae whenever the ulcer comes in contact with water. Larval discharge continues intermittently for as long as 3 weeks until the uterus is empty. The female worm then dies and is either extruded or absorbed. In the absence of secondary infection the ulceration heals in 4-6 weeks from onset.

Clinical effects are produced only by the female worm. Multiple infections occur, but the usual infection is with a single worm. Several hours before the head appears at the skin surface local erythema and tenderness often develop in the area where emergence is to take place. In some patients there may be systemic symptoms at this time, including urticaria, generalized pruritus, nausea, vomiting, and dyspnea. As the blister forms and ruptures these symptoms subside. The tissues surrounding the ulceration which remains after rupture of the blister frequently become indurated, reddened, and tender, and since 90% of the lesions appear on the leg or foot the patient often must give up walking and work. Uninfected ulcers heal in 4-6 weeks, but secondary infection is so common that the course is often prolonged.

Secondary infection is the rule and may cause development of an abscess which eventually involves deep structures. Ankle and knee joint infection and deformity is a common complication in some areas. If the worm is broken during removal sepsis almost always results, leading to cellulitis, abscess formation, or septicemia.

When a worm is not visible in the ulcer the diagnosis may be made by detection of larvae in fluid expressed from the moistened ulcer. A skin test is available, but its value

as a diagnostic aid is not established. Eosinophilia of about 10% often accompanies the symptoms before blister formation. Calcified guinea worms are occasionally revealed as chance findings during x-ray examination of persons in endemic areas.

#### Treatment.

**A General Measures** The patient should be at bed rest with the affected part elevated. Cleanse the lesion and control secondary infection with antibiotics. Apply wet compresses continuously to hasten discharge of all larvae from the uterus of the worm. This may require 1-2 days.

**B Surgical Removal** Make multiple incisions under local anesthesia along the worm tract, and remove the entire worm carefully. This method has the advantage of speed, but the disadvantage that x-ray (using a contrast medium in the tract) is usually necessary to locate the worm. Give antihistamines preoperatively to control allergic symptoms arising from manipulation or rupture of the worm. Before surgery the worm may be killed by injections of mercury bichloride, acriflavine, or chloroform, but this is probably not necessary.

**C Removal by Extraction** With patience this time-honored method is safe and effective, but it has the disadvantage of being slow. The head of the worm is identified and tied to an applicator stick with a thread. The worm is gently wound on the stick, a little at a time. The extraction may require a week or more. The stick and worm should be covered with sterile dressings. Injections of phenothiazine in olive oil (M) are said to cause partial extrusion of the worm and hasten the extraction.

Elliot, M.: A new treatment for dracunculiasis. Trans. Roy. Soc. Trop. Med. & Hyg. 35: 291-301, 1942.

### ONCHOCERCIASIS

Man and *Simulium* black flies are the natural hosts of *Onchocerca volvulus*, a filarial nematode found in many parts of tropical Africa and in localized areas of Central America and northern South America, including southern Mexico, the highlands of Guatemala, and eastern Venezuela. The biting fly introduces infective larvae which develop slowly in the cu-

taneous and subcutaneous tissues of man. Flies are infected in turn by picking up microfilariae while biting. Adult worms may live for years frequently in fibrous nodules which develop around one or more of the parasites. Microfilariae, motile and migratory, may be found in the skin, subcutaneous tissues, lymphatics, the conjunctivas, and other structures of the eye.

Intensity of infection determines the extent and severity of the clinical picture. After an incubation period of several months to one year, skin manifestations appear in up to 40% of patients. Localized or generalized pruritus is common, usually causing scratching and skin excoriation. Pigmentary changes, skin thickening, and lichenification may appear later. Erysipeloid or papulovesicular eruptions are sometimes seen. Subcutaneous nodules develop around adult worms, hence they appear at a later stage of the infection. The nodules, usually painless, consist of fibrous tissue surrounding one or many living or dead worms. Common sites are over bony prominences on the trunk, thighs, shoulders, arms, and head. Few patients have more than 3-6 nodules. The most common early ocular finding is a superficial punctate keratitis. Vascular pannus, iritis, and cyclitis are serious later manifestations. While certain retinal changes, atrophic choroiditis, and optic atrophy are seen in patients with onchocerciasis, some investigators doubt that these lesions are actually due to the infection.

Eosinophilia of 15-50% is common. Aspiration of nodules will usually reveal eggs and microfilariae, and adult worms may be demonstrated in excised nodules. Microfilariae are not found in the blood, but can be identified in skin or conjunctival snips or in skin shavings. The snip is performed by tenting the skin with a needle and cutting off a bit of skin above the needle tip. A blood-free shaving may be cut with a razor blade from the top of a ridge of skin firmly pressed between thumb and forefinger. The snip or shaving is examined in a drop of saline under a coverslip on a slide. Shavings or snips should be taken from several sites over bony prominences of the scapular region, hips, and thighs. In ocular onchocerciasis a slit lamp will usually reveal many microfilariae in the anterior chamber. Complement fixation and skin tests are of doubtful value because of high false-positive reaction rates.

Glaucoma and cataracts arising from iritis and cyclitis may cause blindness. Posterior segment lesions seen in patients with onchocerciasis may also cause blindness.

Surgical removal of nodules is not curative, but removes many adult worms and is particularly justifiable when nodules are located close to the eyes. Nodulectomy may also be indicated for cosmetic reasons.

Diethylcarbamazine (Hetrazan<sup>®</sup>, Banocide<sup>®</sup>) is almost nontoxic and fairly effective. Give 3 mg./Kg. body weight orally t.i.d. for 21 days. To prevent severe allergic symptoms which may be provoked early in therapy as microfilariae are rapidly killed, start treatment with small doses and increase dosage over 3-4 days. When the eyes are involved particular caution is necessary, starting with a single daily dose of 0.25 mg./Kg. Use antihistamines to control allergic symptoms.

One course of diethylcarbamazine will eradicate the infection in about 40% of patients and halt progression in the remainder. Two or 3 courses will cure almost all cases.

Suramin sodium is more effective than diethylcarbamazine in eradicating infection in a single course, but it has the disadvantage of potential renal toxicity (proteinuria, casts, red cells). Renal disease is a contraindication. For adults give 1 Gm. of a 10% solution in distilled water I.V. every 4-7 days to a total dose of 5-10 Gm. Start treatment with a test dose of 0.2 Gm.

With chemotherapy, progression of all forms of the disease usually can be checked. The prognosis is unfavorable only for those patients seen for the first time with already far-advanced ocular onchocerciasis.

Adams, A.R.D., & others: Symposium on onchocerciasis. Trans. Roy. Soc. Trop. Med. & Hyg. 52:95-134, 1958.

## GNATHOSTOMIASIS

Gnathostomiasis is an infection due to the nematode parasite, *Gnathostoma spinigerum*, which is found only in eastern and southern Asia. Dogs and cats are the normal hosts, the crustacean Cyclops and fish serve as intermediate hosts. Man is infected accidentally by eating infected raw fish. In man the immature worm migrates continually until it dies or is removed.

A single migratory subcutaneous swelling is the most common manifestation. The usually painless swelling, caused by the migrating worm, is firm, pruritic, and variable in size. It may appear anywhere on the body surface, remain in that area for days or weeks, or

wander continually. Internal organs, the eye, and the cervix may also be invaded. Occasionally the worm becomes visible under the skin.

Spontaneous pneumothorax, leukorrhea, hematuria, hemoptysis, paroxysmal coughing, and edema of the pharynx with dyspnea have been reported as complications.

A high eosinophilia accompanies the infection. Specific skin testing antigens are available as a diagnostic aid, but final diagnosis usually rests upon identification of the worm.

Surgical removal of the worm when it appears close to the skin surface is the only effective treatment. Chemotherapy has not proved successful, although symptoms may be relieved by the use of diethylcarbamazine (Hetrazan<sup>®</sup>) as for filariasis.

The prognosis is usually good. However, complications such as pneumothorax and pharyngeal edema may be dangerous in the absence of good medical care.

Daengsavan, S.: Human gnathostomiasis in Siam with reference to the method of prevention. J. Parasitol. 35:116-21, 1949.

# ARTHROPOD INFECTIONS

## MYIASIS

Myiasis is infestation with the larvae of various species of flies. Specific myiases, in which the fly larvae are parasitic, developing only in living flesh (e.g., botflies, screw-worm flies), cause the most serious lesions. They are widely distributed (e.g., horse, cattle, and sheep botflies), but a few species are prominent in specific geographic areas, e.g., the flesh-fly *Wohlfahrtia vigil* of the northern United States and adjacent Canada, and the human botfly (*Dermatobia hominis*) in Mexico and tropical South America, which, like the tumbu-fly of Africa (*Cordylobia anthropophaga*) produces large boil-like swellings, and the primary screw-worm (*Callitroga hominivorax*, *Cochliomyia americana*) of tropical and sub-tropical America, which invades tissues with astonishing speed. In the so-called semi-specific myiases, the larvae developing (usually) in decaying flesh may invade wounds or cavities. In intestinal or accidental myiases the larvae or eggs are ingested or the eggs are laid at the body orifices.

Nasal, oral, ocular, and aural myiases are produced by invasion of these tissues by larvae of the primary screw-worm (*C. hominivorax*, warm parts of the Western Hemisphere), the Old World screw-worm (*Chrysomya*, oriental and Ethiopian), sheep botfly (*Oestrus ovis*, world-wide), or flesh-flies (*Wohlfahrtia magnifica*, Mediterranean to U.S.S.R.). Other flies may invade secondarily. There may be extensive tissue destruction.

Intestinal myiasis (various species) is world-wide in distribution, but most cases have been recorded in India. Genitourinary myiasis due to migration of larvae (many species) into the bladder or vagina is rare.

The clinical manifestations are nonspecific, and are ascribable to progressive inflammation, often with great irritation, of the appro-

priate cavity. Gastrointestinal disturbances may include vomiting and melena, and larvae are commonly passed in the feces spontaneously. In the conjunctival sac or lacrimal duct the nasal cavity or sinuses, or the oral cavity, larvae may be seen by appropriate methods.

Removal of larvae by irrigation is frequently made more effective by instilling 5-10% chloroform in milk or light vegetable oil for 30 minutes. This is best done after a preliminary lavage. Continue with appropriate treatment to encourage healing. In intestinal myiasis, victims often also harbor one or more species of helminth. Purges and vermifuges should be accompanied by efforts to minimize further infestation.

### Ocular Myiasis,

Conjunctival infestation with fly larvae occurs frequently in the tropics but is rare in the U.S. Several species of flies have been incriminated. Larvae invade the conjunctival sac and produce a nonspecific inflammatory reaction. If they spread throughout the eye and orbit, the inflammatory reaction and eventual necrosis become severe. Destruction of the orbital contents and bony walls of the orbit with invasion of the meninges may occur.

Extreme itching and irritation are the cardinal symptoms. The conjunctiva is red and excoriated. Numerous elongated white larvae are seen, especially in the fornices.

Treatment consists of mechanical removal of the larvae after first instilling cocaine, which has a paralyzing effect upon them. If the larvae can be removed when they are few in number, the course of the disease is automatically terminated. If they are allowed to multiply, the prognosis is extremely poor inasmuch as they invade the tissues out of reach of any form of treatment. In such cases, destruction of the bony orbital wall and its contents frequently occurs.

James, M. T. • The flies that cause myiasis in man. Dept. Agric. Miscell. Publ. 631, 1947

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## Infectious Diseases: Mycotic\*

Carlyn Holdo

### COCCIDIOIDOMYCOSIS

#### Essentials of Diagnosis

- Influenza-like illness with malaise, fever, backache, headache, and cough
- Pleural pain
- Arthralgia and periarticular swelling of knees and ankles
- Erythema nodosum or erythema multiforme
- Dissemination (rare) may result in meningitis or granulomatous lesions in any or all organs
- X-ray findings vary widely from pneumonitis to cavitation
- Positive skin test, serologic tests useful, spherules containing endospores demonstrable in sputum or tissues

Coccidioidomycosis should be considered in the differential diagnosis of any obscure illness in a patient who has lived in or visited an endemic area. The symptoms of primary coccidioidomycosis resemble those of pneumonitis caused by viral or bacterial infections and other mycotic infections. Extensive pulmonary disease is indistinguishable from some forms of tuberculosis and malignancy. Lesions resulting from dissemination resemble tuberculosis, syphilis, bacterial osteomyelitis, neoplasms, and other mycoses.

#### General Considerations.

Coccidioidomycosis results from the inhalation of arthrospores or mycelial fragments of *Coccidioides immitis*, a fungus which grows in soil in certain arid regions of the southwestern United States, Mexico, and localized areas in Central and South America.

About 60% of infections are subclinical and unrecognized other than by the subsequent development of a positive coccidioidin skin test.

In the remaining cases, symptoms may be of severity warranting medical attention. Fewer than 1% show dissemination, but among these patients the mortality rate is high.

#### Clinical Findings.

**A. Symptoms and Signs.** Symptoms of primary coccidioidomycosis occur in about 40% of infections. These vary from mild to severe and prostrating. The onset (after an incubation period of 10-30 days) is usually that of a respiratory tract illness with fever and occasionally chills. Pleural pain is common and usually severe. Muscular aches, backache, and headache may be severe. Nasopharyngitis may be followed by bronchitis accompanied by a dry or slightly productive cough. Weakness and anorexia may become marked, leading to prostration. A morbilliform rash may appear 1-2 days after the onset of symptoms.

Arthralgia accompanied by periarticular swellings, often of the knees and ankles, is common. Erythema nodosum may appear 2-20 days after onset of symptoms. Erythema multiforme may appear on the upper extremities, head, or thorax. Breath sounds may become bronchial in nature, especially in the severely ill patient. Persistent pulmonary lesions, varying from cavities and abscesses to parenchymal nodular densities or bronchiectasis, occur in about 5% of diagnosed cases.

About 0.1% of the white patients and 1% of the nonwhite are unable to localize or control infection due to *C. immitis*. Symptoms in progressive coccidioidomycosis depend upon the site of dissemination. Any or all organs may be involved. Pulmonary findings usually become more pronounced, with mediastinal and hilar lymph node enlargement, cough, and increased sputum production. Pulmonary abscesses may rupture into the pleural space, producing an empyema. Extension to bones and skin may take place, and pericardial and myocardial extension is not unusual.

Lesions in the bones are often in the bony prominences and the ends of long bones. The ankle, wrist, and elbow joints are commonly involved. Meningitis occurs in about 25% of

\*Superficial mycoses are discussed in Chapter 4.

disseminated cases Subcutaneous abscesses and verrucous skin lesions are especially common in fulminating cases. Lymphadenitis may occur and may progress to suppuration Mediastinal and retroperitoneal abscesses are not uncommon

**B Laboratory Findings** In primary coccidioidomycosis there may be a moderate leukocytosis and eosinophilia The sedimentation rate is elevated, returning to normal as the infection subsides If the sedimentation rate persists or increases, there is danger of progressive disease A coccidioidin skin test becomes positive within 1-3 weeks after onset of symptoms Precipitin antibodies appear in most symptomatic infections but disappear after 1-2 months Complement-fixing antibodies appear later, but persist longer The prognosis is good if this titer falls Demonstrable antibodies in spinal fluid are pathognomonic for coccidioidal meningitis Spinal fluid findings include increased cell count with lymphocytosis and reduced sugar Spherules filled with endospores may be found in clinical specimens These should be cultured only by trained technicians using safety precautions because of the danger of laboratory infection

**C X-ray Findings** X-ray findings vary but patchy and nodular infiltrations are the most common Hilar lymphadenopathy may be visible. There may be primary pleural effusion Thin-walled cavities may appear

#### Complications.

Pulmonary infiltrations persisting for 6 or more weeks should be suspected of possible progression, especially with increase in area, enlargement of mediastinal and hilar nodes, cavity enlargement, and hemoptysis Progressive disease is more likely to appear in Negroes, Filipinos, and Mexicans Pregnant women of any race are also more vulnerable to dissemination

#### Treatment.

Bed rest is the most important therapeutic measure for the primary infection This should be continued until there is a complete regression of fever, a normal sedimentation rate, clearing or stabilization of pulmonary radiologic findings, and a lowering of the complement fixation titer. These precautions are especially important for patients in whom the rate of dissemination is high General symptomatic therapy is given as needed

There is no specific therapy for patients with disseminated disease Amphotericin B (Fungizone®) has proved effective in some pa-

tients and should be tried The drug is suspended in 500 ml of 5% dextrose in distilled water (not saline) and administered 1 V over a 6-8 hour period The adult daily dose is 50 mg, but since this drug has toxic properties (including renal toxicity) therapy should begin with no more than 25 mg daily and then be increased slowly Therapy should be continued for 1-2 months, interrupting or reducing the dosage or giving the drug on alternate days if toxic reactions are noted

Thoracic surgery is indicated for giant, infected or ruptured cavities Surgical drainage is also useful for subcutaneous abscesses Excisional surgery may be used to remove any focus or source of proliferating spherules Amphotericin B should be given for 3-4 weeks before and after surgery

#### Prognosis

The prognosis is good, but persistent pulmonary cavities may present complications Before amphotericin B became available the prognosis for disseminated coccidioidomycosis was poor, with a mortality rate approaching 50%.

Piese, M J. Coccidioidomycosis Thomas 1958

Harrell, E R, & F C Bocobo Modern treatment of the systemic fungus diseases Clin Pharm & Therap 1 104 34, 1960

Wilson, J.W. Therapy of systemic fungous infections in 1961 Arch Int Med 108 292-316, 1961.

## HISTOPLASMOSIS

#### Essentials of Diagnosis

- Asymptomatic to severe respiratory symptoms with malaise, fever, cough, and chest pain
- Ulceration of naso- and oropharynx
- Hepatomegaly, splenomegaly, and lymphadenopathy
- Anemia and leukopenia
- Diarrhea in children
- Positive skin test, positive serologic findings, small budding fungus cells found within reticuloendothelial cells, culture confirms diagnosis.

Tuberculosis as well as most diseases from which it must be differentiated must be considered in the differential diagnosis of histoplasmosis In addition hepatosplenomegaly suggests

amebiasis and leishmaniasis. Lymph node enlargement resembles Hodgkin's disease, leukemia, and lymphosarcoma. The blood findings may suggest various blood dyscrasias or infectious mononucleosis. Oral lesions may resemble syphilis neoplasms leishmaniasis, Vincent's angina, or other fungal infections.

### General Considerations.

Histoplasmosis is caused by *Histoplasma capsulatum*, a fungus which has been isolated from soil in endemic areas (central and eastern United States, eastern Canada, Mexico, Central America, South America, Africa, and Southeast Asia). Infection takes place presumably by inhalation of spores or mycelial fragments. These convert into small budding cells which are engulfed by phagocytic cells in the lungs. The organism proliferates and may be carried by the blood to other areas of the body.

### Clinical Findings

**A. Symptoms and Signs.** Most cases of histoplasmosis are asymptomatic or mild and so are unrecognized. Past infection is recognized by the development of a positive histoplasmin skin test and occasionally by pulmonary and splenic calcification. Symptomatic infections may present mild influenza-like characteristics, often lasting 1-4 days. Signs and symptoms of pulmonary involvement are usually absent even in patients who subsequently show areas of calcification on chest x-ray. Moderately severe infections are frequently diagnosed as atypical pneumonia. These patients have fever, cough, and mild chest pain lasting 5-15 days. Physical examination is usually negative. X-ray findings are variable and nonspecific.

Severe infections have been divided into 3 groups. (1) Acute histoplasmosis frequently occurs in epidemics. It is a severe disease with marked prostration, fever, and occasional chest pain, but no particular symptoms relative to the lungs even when x-rays show severe disseminated pneumonitis. The illness may last from one week to 6 months, but is almost never fatal. (2) Acute progressive histoplasmosis is usually fatal within 6 weeks or less. Symptoms usually consist of fever, dyspnea, cough, loss of weight, and prostration. Diarrhea is usually present in children. Ulcers of the mucous membranes of the oral pharynx may be present. The liver and spleen are nearly always enlarged, and all the organs of the body are involved. (3) Chronic progressive histoplasmosis may continue for years. It is

usually seen in older patients in whom it has been mistaken for tuberculosis. The lungs show chronic progressive changes, often with cavities. The disease closely resembles chronic tuberculosis, and occasionally the patient has both diseases. Chronic histoplasmosis appears to be primarily confined to the lungs, but all organs of the body are involved in the terminal stage.

**B. Laboratory Findings.** In the moderately to severely ill patient the sedimentation rate is elevated. Leukopenia is present, with a normal differential count or neutropenia. Most patients with progressive disease show a progressive hypochromic anemia. Complement-fixing antibodies can be demonstrated, and a change in titer is of use in prognosis.

### Treatment.

There is no specific therapy. Bed rest and supportive care are indicated for the primary form. Normal activities should not be resumed until fever has subsided. Resection of lung tissue containing cavities has been useful. Amphotericin B (Fungizone®) (as for coccidioidomycosis) has proved useful for some patients with progressive histoplasmosis.

### Prognosis.

The prognosis is excellent for primary pulmonary histoplasmosis, only fair in localized infection, and poor in untreated generalized infection.

Loosli, C. G. Histoplasmosis, *J. Chronic Dis* 5 473-88, 1957.

Rubin, H., & others. The course and prognosis of histoplasmosis, *Am J. Med.* 27 278-88, 1959.

### CRYPTOCOCCOSIS (Torulosis)

Cryptococcosis, a chronic disseminated infection which frequently involves the CNS, is caused by *Cryptococcus neoformans*. This is an encapsulated, budding, yeast-like fungus which has been found in soil and in pigeon nests. Human infection is world-wide.

It is believed that most infections are acquired by inhalation. In the lung the infection may remain localized, heal, or disseminate. Upon dissemination lesions may form in any part of the body, but involvement of the CNS is most common and is the usual cause of death. Generalized meningoencephalitis oc-



curs more frequently than localized granuloma in the brain or spinal cord. Solitary localized lesions may develop in the skin and rarely in the bones and other organs.

Cryptococcosis was at one time believed to be invariably fatal, but some cases (especially pulmonary) of spontaneous resolution have been reported. The incidence of fatal cases, on the other hand, is increasing as a result of increased numbers of infections in susceptible debilitated individuals.

In pulmonary cryptococcosis there are no specific signs or symptoms, and many patients are nearly asymptomatic. The patient may present a subacute respiratory infection with low-grade fever, pleural pain, and cough. There may be sputum production. Physical examination usually reveals signs of bronchitis or pulmonary consolidation. X-rays commonly show a solitary, moderately dense infiltration in the lower half of the lung field, with little or no hilar enlargement. More diffuse pneumonic infiltration, also in the lower lung fields, or extensive peribronchial infiltration or millary lesions, may also occur.

CNS involvement usually presents a history of recent upper respiratory or pulmonary infection. Increasingly painful headache is usually the first and most prominent symptom. Vertigo, nausea, anorexia, ocular disorders, and mental deterioration develop. Nuchal rigidity is present, and Kernig's and Brudzinski's signs are positive. Patellar and Achilles reflexes are often diminished or absent.

Cutaneous lesions are variable in appearance. Acanthomycotic lesions are more commonly seen. These enlarge slowly and ulcerate, often coalescing with other lesions to cover a large area. Bone lesions are painful, and the area is often swollen. Eye involvement may result from direct extension along the sub-arachnoid space into the optic nerve.

A mild anemia, leukocytosis, and increased sedimentation rate are found. Spinal fluid findings include increased pressure, many white cells (usually lymphocytes), budding encapsulated fungus cells, increased protein and globulin, and decreased sugar and chlorides. The organism is readily seen in an India ink preparation.

There is no specific therapy for cryptococcosis. Amphotericin B (Fungizone<sup>®</sup>) (as for coccidioidomycosis) has been successful in some cases when therapy was begun before extensive involvement of the CNS took place. Surgical resection of pulmonary granulomas has been successful.

Littman, M. L.: Cryptococcosis. Current concepts and therapy. *Am. J. Med.* 27:976-98, 1959.

## NORTH AMERICAN BLASTOMYCOSIS

*Blastomyces dermatitidis* causes this chronic systemic fungus infection. Because most infections have a history of pulmonary lesions, infection probably takes place following inhalation of fungus-laden dust. The disease occurs more often in men and in a geographically delimited area of central and eastern United States and Canada (rarely in Mexico).

Mild or asymptomatic cases have not been found. When dissemination takes place, lesions are most frequently seen on the skin, in bones, and in the CNS although any or all organs of the body may be attacked.

Little is known concerning the mildest pulmonary phase of this disease. Cough, moderate fever, dyspnea, and chest pain are evident in symptomatic patients. These may disappear or may progress to a marked degree with bloody and purulent sputum production, pleurisy, fever, chills, loss of weight and prostration. Radiologic studies usually reveal massive densities projecting irregularly from the mediastinal nodes, which are markedly enlarged. Raised, verrucous cutaneous lesions which have an abrupt downward sloping border are usually present in disseminated blastomycosis. The surface is covered with millary pustules. The border extends slowly, leaving a central atrophic scar. In some patients only cutaneous lesions are found. These may persist untreated for long periods, with a gradual decline in the patient's health. Bones - often the ribs and vertebrae - are frequently involved. These lesions appear both destructive and proliferative on x-ray. Symptoms referable to CNS involvement appear in about one-third of cases. The viscera may be invaded, but rarely the gastrointestinal tract.

Laboratory findings usually include leukocytosis, hypochromic anemia, and elevated sedimentation rate. The organism is found in clinical specimens as a 5-20 $\mu$ , thick-walled cell which may have a single bud. It grows readily on culture. Complement-fixing antibody titer is useful for prognosis.

There is no specific therapy for blastomycosis. Amphotericin B (Fungizone<sup>®</sup>) (as for coccidioidomycosis) appears to be the best drug available for treatment. Hydrocortisone, desensitization with an autogenous

vaccine, and iodide therapy have proved effective in some cases. Surgical procedures may be successful for the removal of cutaneous lesions, persistent cavities or other localized pulmonary lesions.

Blastomycosis is a serious disease. Careful follow-up for early evidence of relapse should be made for several years so that Amphotericin B therapy may be resumed. Patients whose disease is limited to localized cutaneous lesions have the best prognosis in that they show a better immunologic response to their infection.

Baum, G. L., & J. Schwarz. North American blastomycosis. *Am J Med Sc* 238 661 83 1959

Harrell, E. R., & A. C. Curtis. North American blastomycosis. *Am J Med* 27 750 66, 1959

### SOUTH AMERICAN BLASTOMYCOSIS

*Blastomyces (Paracoccidioides) brasiliensis* infections have been found only in patients who have resided in South or Central America.

Ulceration of the naso- and oropharynx is usually the first symptom. Papules ulcerate and enlarge both peripherally and deeper into the subcutaneous tissue. Extensive coalescent ulcerations may eventually result in destruction of the epiglottis, vocal cords, and uvula. Extension to the lips and face may occur. Eating and drinking are extremely painful. Skin lesions, usually on the face, may occur. Variable in appearance, they may have a necrotic central crater with a hard hyperkeratotic border. Lymph node enlargement always follows mucocutaneous lesions, eventually ulcerating and forming permanent draining sinuses. Lymph node enlargement may be the presenting symptom, with subsequent suppuration and rupture through the skin. In some patients gastrointestinal disturbances are first noted. Although the liver and spleen become enlarged, there is a lack of specific gastrointestinal symptoms. Cough, sometimes with sputum, indicates pulmonary involvement, but the signs and symptoms are often mild, even though x-ray findings indicate severe parenchymatous changes in the lungs.

The extensive ulceration of the entire gastrointestinal tract prevents sufficient intake and absorption of food. Most patients become cachectic early. Death usually results from associated malnutrition.

Laboratory findings include elevated sedi-

mentation rate, leukocytosis with a neutrophilia showing a shift to the left, and sometimes eosinophilia and monocytosis. Serologic results are variable. A high titer usually indicates progressive disease, a descending titer is a favorable sign. The fungus is found in clinical specimens as a spherical cell which may have many buds arising from it. Colonial and cellular morphology are typical on culture.

The prognosis for South American blastomycosis has been poor. Amphotericin B (Fungizone<sup>®</sup>) (as for coccidioidomycosis) has been used recently with considerable success. Sulfadiazine and triple sulfonamides in daily doses of 2-4 Gm. have been used for control and occasional cures have been reported following months or years of therapy. Relapses are frequent when the drug is stopped. Drug toxicity with prolonged high dosage is common. Rest and supportive care are of value in promoting a favorable immunologic response.

### CANDIDIASIS (Moniliasis)

*Candida albicans* may be cultured from the mouth, vagina, and feces of about 20% of the population. It is more frequent in debilitated individuals. Thrush, perleche, vaginitis, cutaneous lesions (frequently in intertriginous areas), onychia, and paronychia are common. Systemic infection, especially bronchial or pulmonary disease, is usually found in patients with a history of other pulmonary disorders, diabetes mellitus, or general debilitation or in those who have undergone prolonged antibiotic therapy. *Candida albicans* is a frequent secondary invader in other types of infection.

Mucous membrane and cutaneous infections are discussed elsewhere in this book. Bronchial candidiasis is mild with persistent cough and sputum production. X-ray shows nonspecific peribronchial thickening. Pulmonary disease is more serious, with fever, night sweats, chest pain and occasional pleural effusion. Cough becomes more productive. Hemoptysis occasionally occurs. Two or more lobes may be involved. The characteristic signs of bronchial pneumonia or lobar pneumonia develop as the disease progresses. The severity of the disease can be judged by the size and extent of the lesions on x-ray.

Systemic infection may follow recalcitrant skin, oral, or gastrointestinal infections, and is often associated with other serious debilitating conditions. Blood stream invasion may result in vegetations on the heart valves.

meningitis, and brain abscesses, as well as lesions in the kidney and other organs.

*Candida albicans* is seen in sputum as gram-positive budding cells (2.5-6 $\mu$ ) and as a pseudomycelium. It grows readily in culture. Only when *C. albicans* is present in large numbers in fresh sputum and the patient has no oral lesions can the diagnosis of bronchial or pulmonary candidiasis be entertained. Justification must include ruling out all other possible causes of pulmonary disease, since *C. albicans* is a frequent secondary invader.

I.V. administration of amphotericin B (Fungizone<sup>®</sup>) (as for coccidioidomycosis) is necessary in serious pulmonary and systemic infections. Associated oral, gastrointestinal, and cutaneous lesions should be treated with amphotericin B (Fungizone<sup>®</sup>) or nystatin (Mycostatin<sup>®</sup>) mouthwash, tablets (500,000 units t.i.d.), and lotions. Gentian violet, 1%, in 10-20% alcohol, is also effective for oral, cutaneous, and vaginal lesions. Antibiotic therapy should be discontinued if possible. The correction of underlying factors may be sufficient to control candidiasis without specific therapy. All patients with candidiasis should be carefully examined for diabetes mellitus.

The prognosis is good if the underlying predisposing factors are corrected.

- Dobias, B.: Moniliasis in pediatrics. *Am. J. Dis. Child.* 94:234-51, 1957.  
 Louria, D. B., & P. Dineen: Amphotericin B in treatment of disseminated moniliasis. *J.A.M.A.* 174:273-8, 1960.

## NOCARDIOSIS

Nocardiosis includes a variety of diseases caused by the actinomycetes, *Nocardia asteroides* and *N. brasiliensis*, and several species of *Streptomyces* formerly classified as *Nocardia*. These organisms are normal inhabitants of soil. Infection takes place by accidental introduction into the skin or by inhalation. Nocardiosis is world-wide in distribution, and infection has been recorded in many animals. When introduced into the skin, any of these fungi may produce an indurated lesion in which abscesses form and drain to the exterior (mycetoma). Pulmonary infection is caused only by *Nocardia asteroides*. Subsequent dissemination may involve all organs.

Pulmonary involvement usually begins with malaise, loss of weight, fever and night sweats. Cough and production of purulent sputum are the chief complaints. X-ray

shows massive areas of consolidation, usually at the base of both lungs. Small areas of rarefaction caused by abscess formation within these consolidated masses may lead to multiple cavities. The lesions may penetrate to the exterior through the chest wall, invading the ribs. Pleural adhesions are common.

Dissemination may involve any organ. Lesions in the brain or meninges are most frequent, and such dissemination may occur following any minor pulmonary symptoms. Dissemination is common in debilitated patients.

An increased sedimentation rate and leukocytosis with increase in neutrophils are found in systemic nocardiosis. *N. asteroides* is usually found as delicate, branching, gram-positive filaments which may be partially acid-fast. In mycetoma the various *Nocardia* species are usually found as granules in pus. Species identification is made by culture.

Nocardiosis generally responds to 4-6 Gm of sulfadiazine daily. This may be increased to 8-9 Gm in severely ill patients. Sensitivity tests should be used to determine the appropriate antibiotic, which should be administered concurrently in large dosage. Response is slow, and therapy should be continued for several months after all clinical manifestations have disappeared. Surgical procedures such as drainage and resection may be imperative.

The prognosis for systemic nocardiosis is poor when diagnosis and therapy are delayed.

- Murray, J. F., & others: The changing spectrum of nocardiosis. *Am. Rev. Resp. Dis.* 83:315-30, 1961.

## ACTINOMYCOSIS

*Actinomyces israeli* (*A. bovis*) occurs in the normal flora of the mouth and tonsillar crypts. It is an anaerobic, gram-positive, branching filamentous organism resembling bacteria in that the filaments (1 $\mu$  in diameter) readily fragment into bacillary forms. In diseased tissue these filaments are seen as a compact mass called a "sulfur granule." When introduced into tissue and associated with bacteria, *A. israeli* becomes a pathogen. Hard, indurated, granulomatous, suppurative lesions develop which give rise to sinus tracts.

The most common site of infection is the cervicofacial area (about 60% of cases), and infection typically follows extraction of a tooth or other trauma. Lesions may develop in the

gastrointestinal tract or lungs following ingestion or inhalation of the fungus from its endogenous source in the mouth

Cervicofacial actinomycosis develops slowly. The area becomes markedly indurated and the overlying skin becomes reddish or cyanotic. The surface is irregular. Abscesses developing within and eventually draining to the surface persist for long periods. Sulfur granules may be found in the pus. There is usually little pain unless there is marked secondary infection. Trismus indicates that the muscles of mastication are involved. X-ray reveals eventual involvement of the bone with rarefaction as well as some proliferation of the underlying bone.

Abdominal actinomycosis usually causes pain in the ileocecal region, spiking fever and chills, intestinal colic, vomiting and weight loss. Irregular masses in the ileocecal area or elsewhere in the abdomen may be palpated. Sinuses draining to the exterior may develop. X-ray may reveal the mass or enlarged viscera. Vertebrae and pelvic bones may be invaded.

Thoracic actinomycosis begins with fever, cough and sputum production. The patient becomes weak, loses weight, may have night sweats and dyspnea. Pleural pain may be present. Dysphagia can result from mediastinal involvement. Multiple sinuses may extend through the chest wall to the heart or into the abdominal cavity. Ribs may be involved. X-ray shows massive areas of consolidation, frequently at the bases of the lungs.

The sedimentation rate may be elevated in patients with progressive disease. Anemia and leukocytosis are usually present. The anaerobic gram positive organism may be demonstrated as a granule or as scattered branching gram positive filaments in the pus. Anaerobic culture is necessary to distinguish *A. israeli* from *Nocardia* species. Specific identification by culture is necessary to avoid confusion with nocardiosis because specific therapy differs radically.

Penicillin is the drug of choice. One to 6 million units are given I/M each day for at least 6-8 weeks. In severe infection as much as 12 million units/day may be given. Prolonged massive therapy is necessary in order to push effective levels of the drug into the abscesses where the organism is found. Sulfonamides may be added to the regimen as well as streptomycin which will control associated gram negative organisms. Broad-spectrum antibiotics should be considered only if sensitivity tests show that the organism is resistant to penicillin. Immediate amelioration of symptoms or prompt improvement cannot be expected because of the chronic nature

of this disease. Therapy should be continued for weeks to months after clinical manifestations have disappeared in order to ensure cure. Surgical procedures such as drainage and resection are of great benefit.

With penicillin and surgery the prognosis is good. The difficulties of diagnosis, however, may permit extensive destruction of tissue before therapy is started.

Peabody, J. W. & J. H. Seabury. Actinomycosis and nocardiosis. A review of basic differences in therapy. *Am J Med* 28:93, 1960.

## SPOROTRICHOSIS

Sporotrichosis is a chronic fungal infection caused by *Sporotrichum schenckii*. It is world wide in distribution; most patients are people whose occupation brings them in contact with soil, plants, or decaying wood. Infection takes place when the organism is introduced by trauma into the skin, often on the hand, arm or foot.

The most common form of sporotrichosis begins with a hard, nontender subcutaneous nodule. This later becomes adherent to the overlying skin, ulcerates (chancreiform) and may persist for a long time. Within a few days to weeks similar nodules usually develop along the lymphatics draining this area, and these may ulcerate. The lymphatic vessels become indurated and are easily palpable. The infection usually ceases to spread before the regional lymph nodes are invaded and blood borne dissemination is rare. The general health of the patient is not affected. Some patients complain of considerable pain. Skin infection may not spread through the lymphatics but may appear only as warty or papular scaly lesions which may become pustular.

Pulmonary sporotrichosis presents no characteristic findings. Patients may be asymptomatic although pleural effusion, hilar adenopathy, fibrosis, caseous nodularity and cavitation have been reported.

Disseminated sporotrichosis presents a picture of multiple, hard subcutaneous nodules scattered over the body. These become soft but rarely rupture spontaneously. Lesions may also develop in the bones, joints, muscles, and viscera.

There are no specific laboratory findings. Cultures are necessary to establish the diagnosis. A skin test with heat-killed vaccine or sporotrichin is positive.

Potassium iodide taken orally in increasing dosage promotes rapid healing, although the drug is not fungicidal. Give as the saturated solution, 5 drops t.i.d., after meals, increasing by 1 drop per dose until 40 drops t.i.d. are being given. Continue for 2 weeks or until signs of the active disease have disappeared. The dosage is then decreased by one drop per dose until 5 drops are being given, and then is discontinued. Care must be taken to reduce the dosage if signs of iodism appear. Amphotericin B (Fungizone®) I.V. (as for coccidioidomycosis) has been effective in systemic infection. Griseofulvin (Grifulvin®), 1-2 Gm. orally per day, has been reported to be effective in localized lymphatic sporotrichosis. Surgery is usually contraindicated except for simple aspiration of secondary nodules.

The prognosis is good for all forms of sporotrichosis except the disseminated type, when decreased natural resistance probably plays a role.

Scott, S.M., Pessley, E.D., & T.P. Crymes: Pulmonary sporotrichosis. Report of 2 cases with cavitation. New England J. Med 265:453-7, 1961.

### CHROMOBLASTOMYCOSIS

Chromoblastomycosis is a chronic, principally tropical fungal infection caused by several species of closely related fungi having a dark mycelium [Cladosporium (Hormodendrum) spp. and Phialophora sp.]. In nature these fungi grow as filamentous saprophytes in soil and on decaying vegetation.

The disease progresses slowly before the development of clinically characteristic lesions.

Lesions occur most frequently on a lower extremity, but may occur on the hands, arms, and elsewhere. The lesion begins as a papule or ulcer. Over a period of months to years the lesions enlarge to become vegetating, papillomatous, verrucous, elevated nodules with a cauliflower-like appearance or widespread dry verrucous plaques. The latter lesions spread peripherally with a raised, verrucous border leaving central atrophic scarring. The surface of the active border contains minute abscesses. Satellite lesions may appear along the lymphatics. There may be extensive secondary bacterial infection with a resulting foul odor. Some patients complain of itching. Elephantiasis may result if there is marked fibrosis and lymph stasis in the limb.

The fungus is seen as brown, thick-walled, spherical, sometimes septate cells in pus. The type of spore formation found in culture determines the species.

Surgical excision and skin grafting have been necessary in the past, however, 5 mg. of amphotericin B (Fungizone®) per ml. of 2% procaine injected directly into the lesion several times a week has proved curative. Tattooing a solution of amphotericin B into the lesion with a vibrapuncture apparatus has also resulted in cure. Potassium iodide (as for sporotrichosis) and calciferol (50,000 units twice a week) have been reported to be useful in early cases when there is little fibrosis.

The prognosis is favorable if the disease is diagnosed and treated in its early stages.

Costello, M.J., De Feo, C.P., & M.L. Littman: Chromoblastomycosis treated with local infiltration of amphotericin B solution. Arch. Dermat. 79:184-90, 1959.

### MYCETOMA

(Maduromycosis & Actinomycotic Mycetoma)

Maduromycosis is the term used to describe mycetoma caused by the higher fungi. Actinomycotic mycetoma is caused by Nocardia and Streptomyces sp. The many species of causative fungi are found in soil. Organisms are introduced by trauma in barefoot people. Mycetoma may occur on the hand and other parts of the body also. With time, the subcutaneous lesions develop sinuses which drain to the surface as well as deep into muscle and bone. The fungus is compacted into a granule which drains out in the pus.

The disease begins as a papule, nodule, or abscess which over months to years progresses slowly to form multiple abscesses and sinus tracts ramifying deep into the tissue. The entire area becomes indurated, and the skin becomes discolored. Open sinuses or atrophic scars are scattered over its surface. Secondary bacterial infection may result in large open ulcers. When x-rayed, destructive changes are seen in the underlying bone. Extensive fibrosis in the tissue causes elephantiasis. Pain is not a serious complaint until the disease is far advanced.

The fungus occurs as white, yellow, red, or black granules in the tissue or pus. Microscopic examination assists in the diagnosis. The granules of Nocardia and Streptomyces consist of delicate, gram-positive branching

filaments  $1\mu$  in diameter. Maduromycosis caused by the higher fungi has granules consisting of hyphae  $5\mu$  in diameter interspersed with large thick-walled chlamydospores.

The prognosis is good for patients with actinomycotic mycetoma since they usually respond well to sulfonamides and sulfones especially if treated early. Give sulfadiazine or triple sulfonamides 4-5 Gm daily, and increase to 10-12 Gm daily if the patient is able to tolerate this dosage. Diaminodiphenylsulfone (Avlosulfon<sup>®</sup>), 100 mg twice daily after meals or other sulfones have been reported to be effective. Griseofulvin (Grifulvin<sup>®</sup>) in daily oral dosage of 1-2 Gm has also been

reported to be curative. All of these medications must be taken for long periods of time and continued for several months after clinical cure to prevent a relapse. Surgical procedures such as drainage assist greatly in healing.

There is no specific therapy for maduromycosis and at present the prognosis is poor. Sulfones have been reported to be effective in isolated cases. Surgical excision of early lesions may prevent spread. Amputation is necessary in far-advanced cases.

Cockshott W P & A M Rankin. Medical treatment of mycetoma. *Lancet* 2 1112-4 1960

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 Emmons C W (editor). *Second Conference*

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# Collagen Diseases & Diseases of Unknown Etiology

Milton J. Chotton

## COLLAGEN DISEASES

A variety of names (e.g., collagen diseases, diffuse vascular diseases, visceral angitides, and diffuse connective tissue diseases) have been given to a group of diseases which appear to have in common a pathologic involvement of mesenchymal tissues. Rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, periarteritis (polyarteritis) nodosa, scleroderma, dermatomyositis, and glomerulonephritis are the chief members of this group of rather ill-defined but probably interrelated diseases of unknown etiology. The differentiation of these disorders into definite clinical categories is often very difficult, and in many instances the diagnosis can be established only after prolonged painstaking observation.

Anatomic, histologic, and immunologic findings often overlap in the collagen diseases.

There is some evidence that hyperimmune reactions (e.g., to drugs, chemicals, and infections) play a contributing role in etiology, although the pathologic reaction in the connective tissues is probably caused by a wide variety of as yet undetermined agents. The fact that several of the collagen diseases are associated with auto-immune responses provides information of great speculative interest regarding the pathogenesis of these disorders. Genetic factors must certainly be considered as contributing to the auto-immune states in which the immune mechanism of a given individual may paradoxically injure or even destroy his own specific tissues.

Rheumatic fever, rheumatoid arthritis, and glomerulonephritis are discussed in other sections of this book.

## SYSTEMIC (DISSEMINATED) LUPUS ERYTHEMATOSUS

### Essentials of Diagnosis

- Occurs predominantly in young women
- Symptoms and signs referable to multiple organ systems
- Weakness, malaise, fever, and weight loss
- Erythematous rash on face or other areas exposed to sunlight
- Anemia, leukopenia, hyperglobulinemia, and increased ESR.
- LE cells may be demonstrated in blood and other tissues

Since systemic lupus erythematosus involves many organ systems it may be confused with a wide variety of diseases, especially musculoskeletal, dermatologic, and hematologic disorders. It must also be differentiated from many acute and chronic infectious diseases.

### General Considerations.

Systemic lupus erythematosus is a non-infectious inflammatory disease which primarily involves the vascular and connective tissues of many organs with a resultant multiplicity of local and systemic manifestations. Although the etiology is not known, the disease may be initiated or aggravated by the use of drugs or foreign proteins or exposure to solar or ultraviolet radiation, and possibly by psychic trauma. An auto-immune mechanism is suggested by the finding of several abnormal protein fractions in the serum of patients with

systemic lupus erythematosus Pathologic changes are usually nonspecific, but include widespread vascular and perivascular fibrinoid changes, disseminated arteritis, verrucous endocarditis, and focal or diffuse glomerulonephritis. Polyserositis and generalized lymphadenitis are found in over 50% of cases. The most characteristic histologic findings are the so-called lupus erythematosus (LE) cells and the apparently related extracellular masses of homogeneous purple nuclear breakdown material (hematoxylin bodies).

### Clinical Findings

#### A Symptoms and Signs

1 Acute - The onset is rapid and the course is fulminant. Prostration, fever, symmetric malar erythema ("butterfly rash"), generalized lymphadenopathy, basilar pneumonia, pleural effusion, tachycardia, gallop rhythm, pericarditis, hepatosplenomegaly, nephritis, musculoskeletal aches and pains, delirium, psychosis, convulsions, coma, and finally death may occur within a few weeks.

2 Chronic - In occasional instances the onset is rapid and the disease later becomes chronic, but most frequently the onset is insidious and the disease is subject to remissions and exacerbations over a period of many years.

(1) Systemic reaction: Weakness, malaise, fever, and weight loss may occur.

(2) Skin: Discoid lupus erythematosus may occasionally precede the systemic focus of the disease. Conversely, discoid lesions may develop during the course of the systemic disease. Erythema of exposed surfaces, especially symmetric malar erythema, is the most common manifestation of systemic lupus erythematosus, but purpura, subcutaneous nodules, angioneurotic edema, alopecia, vitiligo, or hyperpigmentation may occur.

(3) Lymph nodes: Half of patients have generalized lymphadenopathy.

(4) Lungs: Pleurisy, with or without effusion, is common.

(5) Cardiovascular system: Pericarditis, with or without effusion, may occur. Myocarditis with tachycardia, gallop rhythm, and disturbances of rhythm may result in heart failure. Raynaud's phenomenon is common, and gangrene may occur.

(6) Gastrointestinal system: There may be anorexia, nausea and vomiting, diarrhea, abdominal pains, and bloody stools. Hepatomegaly occurs in about one-third of patients, splenomegaly is less common.

(7) Kidneys: Early, a focal glomerulitis may produce only a mild pyuria. This may later progress through the subacute and terminal phases of glomerulonephritis.

(8) Musculoskeletal system: Myalgia and arthralgia occur in almost all patients. About one-third of patients will develop a polyarthritides which is indistinguishable from rheumatoid arthritis.

(9) CNS: Involvement of the CNS may vary from mild neurotic traits to psychosis, convulsions, or coma.

B Laboratory Findings: A mild to moderate normochromic normocytic anemia is found in the majority of patients. Hemolytic anemia occurs infrequently, but may be severe. Mild leukopenia with "shift to the left" is common. The sedimentation rate is high in almost all cases, often even during periods of remission. Serum globulin is increased in about 50% of cases, usually in the alpha<sub>2</sub> and gamma fractions. Many other serum protein abnormalities of unknown significance have been described. Liver function tests are frequently abnormal. Biologic false positive STS are found in 20% of cases. Protein, white cells, red cells, and casts in the urine reflect the type and degree of renal involvement.

Finding the characteristic LE cell in venous blood or in other tissues may be of considerable value in diagnosis, although the LE cell is not pathognomonic. An absence of LE cells does not rule out the diagnosis of systemic lupus erythematosus. The LE cell, which is apparently due to a factor in the plasma of patients with systemic lupus erythematosus, is typically a polymorphonuclear leukocyte containing a large globular mass of homogeneous reddish purple material (when stained with Wright's stain) which fills a large portion of the cell. This material may also occur extracellularly.

### Treatment.

A Corticosteroids and Corticotropin (See p 583.) These drugs may exert a very favorable and often remarkable effect, but the results are variable. Treatment is usually more effective in the early phases of the illness. Many patients obtain marked temporary benefits during acute episodes or when there is involvement of vital organs. Large doses may be necessary, and may be life-saving. Opinion still differs about whether these drugs should be withdrawn after acute attacks subside or continued indefinitely on a maintenance basis.



**B. Other General Measures:** A high-caloric, high-vitamin diet is advised. Iron salts or blood transfusions may be necessary to correct anemia. Patients should be advised against undue exposure to sunlight or to other ultraviolet radiation. If Raynaud's phenomenon exists, protect against exposure to cold. Appropriate anti-infective treatment should be instituted for pneumonia or other infections. Salicylates and other analgesics and physical therapy may be indicated in the management of musculoskeletal aches and pains. Renal disease is treated according to the type and severity of the involvement.

#### Course & Prognosis.

The disease may be fulminant, with a rapid progression of severe symptoms leading to death in a few weeks even with treatment. More frequently, the disease follows an episodic pattern with recurrent involvement of one or more organ systems over a period of many years. Longevity of patients with the chronic illness may be increased by proper corticosteroid therapy.

Dubois, E. L.: Current therapy of systemic lupus erythematosus. A comparative evaluation of corticosteroids and their side-effects with emphasis on fifty patients treated with dexamethasone. *J. A. M. A.* 173:1633-40, 1960.

Holman, H. R.: The L. E. cell phenomenon. *Advances Int. Med.* 10:231-42, 1960.

Larson, D. L.: Systemic Lupus Erythematosus. Little, Brown, 1961.

McCombs, R. P., & J. F. Patterson: Factors influencing the course and prognosis of systemic lupus erythematosus. *New England J. Med.* 260:1195-1204, 1959.

### PERIARTERITIS (POLYARTERITIS) NODOSA

#### Essentials of Diagnosis.

- Symptoms and signs referable to multiple organ systems.
- Weakness, malaise, fever, weight loss.
- Renal involvement, hypertension, asthma, heart failure, cutaneous eruptions, abdominal pain, musculoskeletal aches and pains, peripheral neuritis.
- Proteinuria and hematuria, leukocytosis, eosinophilia, elevated sedimentation rate, hyperglobulinemia.
- Biopsy of painful areas may show necrotizing arteritis.

Since periarteritis nodosa involves the blood vessels of many organ systems it may be confused with many diseases, especially musculoskeletal, dermatologic, hematologic, and other collagen disorders. It must also be differentiated from many acute and chronic infections.

#### General Considerations.

Periarteritis nodosa is a noninfectious inflammatory disease of unknown etiology with varying manifestations of multiple organ systems characterized by widespread segmental inflammation of small and medium-sized arteries. In a few cases there is a history of drug sensitization. The arterial lesions occur most frequently in the kidneys, muscles, peripheral nerves, heart, gastrointestinal tract, and liver, although any organ may be involved. Microscopically, there is a segmental necrosis, fibrous changes, and leukocytic infiltration, with or without eosinophils.

#### Clinical Findings.

**A. Symptoms and Signs:** The mode of onset, clinical findings, and the course of the disease may be highly variable. The most common findings are hypertension, renal disease, musculoskeletal aches and pains, and peripheral neuritis. Other manifestations include fever, malaise, weakness, weight loss, bronchial asthma, bronchial pneumonia, angina, congestive failure, nausea, abdominal pain, hematemesis, and melena. Skin lesions may include papular eruptions, purpura, vesicles, bullae, or subcutaneous periarterial nodules.

**B. Laboratory Findings:** Leukocytosis and mild normocytic anemia are common. Eosinophilia may occur but is not so characteristic as was formerly supposed. The sedimentation rate and the serum globulin level are frequently elevated. Proteinuria, hematuria, pyuria, and casts are common urinary findings.

Biopsy of multiple sections of muscle from painful areas may establish the diagnosis, although negative pathologic findings do not necessarily rule out the possibility of the disease.

#### Differential Diagnosis.

The diagnosis of periarteritis is suggested by the very multiplicity of clinical involvement. Periarteritis must be differentiated from the other angitides such as systemic lupus erythematosus, scleroderma, and Wegener's granulomatosis, and from rheumatic fever, rheumatoid arthritis, glomerulonephritis, and

pyelonephritis it may at times be confused with acute and chronic infections the lymphomas and other granulomatous diseases

### Treatment

Treatment is symptomatic and supportive Corticotropin and the corticosteroids may occasionally be beneficial Intercurrent infections may be treated with antibiotics

### Prognosis

The disease usually runs a fulminating course with death often occurring within a few months after diagnosis In occasional instances the patient may live comfortably for several years especially with corticosteroid therapy

Dahl E V Baggenstoss A H & J H

DeWeerd Testicular lesions of periarthritis nodosa with special reference to diagnosis Am J Med 28 222 8 1960

Nuzum J W Jr & J W Nuzum Sr

Polyarteritis nodosa Statistical review of 175 cases from the literature and report of a typical case Arch Int Med 94 942 55 1954

Report to the Medical Research Council by the Collagen Diseases and Hypersensitivity Panel Treatment of polyarteritis nodosa with cortisone results (1) after one year and (2) after three years Brit M J 1 608 11 1957 and 1 1398 1400 1960

Myocardial involvement may result in arrhythmias or congestive heart failure The sedimentation rate and serum globulin are elevated Renal involvement is common and may lead to terminal uremia Proteinuria hematuria and casts are found frequently in later stages of the disease X rays show subcutaneous calcification osteoporosis of bone and destruction of the distal phalanges Gastrointestinal x rays may show a loss of normal peristalsis

Treatment is symptomatic and supportive Corticosteroids may be tried but they are usually ineffective

The condition is usually slowly progressive for many years Death is usually due to renal or cardiac failure

Biegelman P M Goldner F & T B

Bayles Progressive systemic sclerosis (scleroderma) New England J Med 249 45 58 1953

Farmer R G Gifford R W Jr & E A

Hines Jr Prognostic significance of Raynaud's phenomenon and other clinical characteristics of systemic scleroderma A study of 271 cases Circulation 21 1089 95 1960

Leinwand I Duryee A W & M N Richter

Scleroderma (based on a study of over 150 cases) Ann Int Med 41 1003 41 1954

## DERMATOMYOSITIS

### DIFFUSE SCLERODERMA

Scleroderma is a chronic mesenchymal disease of undetermined origin characterized by connective tissue proliferation in the dermis and in multiple internal organs The onset is insidious stiffness of the hands sweating of the hands and feet and Raynaud's phenomenon may be present for years before the condition becomes recognized The skin eventually becomes hard thick parchment like and glossy without evidence of pitting edema and the fingers and toes become fixed in position Gradually the entire integument becomes involved and ulceration pigmentation and widespread or local calcification of the skin (especially around the joints) may occur Esophageal involvement with dysphagia may occur early Respiratory movement may be impaired as a result of sclerodermatous constriction of the thorax and pulmonary fibrosis and recurrent bronchial pneumonia may occur

Dermatomyositis is a chronic nonpurpurative inflammatory disease of undetermined origin which involves primarily the skin and striated muscles There is an unexplained high incidence of associated neoplastic disease in patients with dermatomyositis

The onset although usually insidious may at times be acute Weakness fatigue mild fever weight loss and muscular aching are early symptoms Diffuse erythema of the face and neck may occur and a purplish periorbital edema is often noted Erythema with or without edema may occur in other skin areas especially the extensor surfaces of the arms and legs Desquamation pigmentary changes and subcutaneous calcification may occur Aching tenderness and weakness of muscles is characteristic Muscular involvement may be generalized but is most marked in the proximal muscles of the upper and lower extremities Involvement of specific muscle groups may result in ocular palsies dysphagia or respiratory embarrassment Multiple gastrointestinal ulcers may occur There

may be a mild normocytic anemia, increased sedimentation rate, and increased serum globulin. Creatinuria parallels muscle destruction. Biopsies show variable dermatitis and nonsuppurative inflammatory, degenerative changes in muscles.

Treatment is symptomatic and supportive. Corticosteroids occasionally provide marked improvement.

The disease is usually moderately progressive and crippling over a period of years, but it may at times be fulminating in nature.

Appropriate investigations to rule out malignant neoplastic disease are indicated for all patients who develop dermatomyositis in adult life.

Everett, M. A., & A. C. Curtis: Dermatomyositis: a review of 19 cases in adolescents and children. *Arch. Int. Med.* 100 70-6, 1957.

Walton, J. N., & R. D. Adams: Polymyositis. Williams & Wilkins, 1958.

Williams, R. C., Jr.: Dermatomyositis and malignancy; a review of the literature. *Ann. Int. Med.* 50 1174-81, 1959.

### NODULAR PANNICULITIS (Weber-Christian Disease)

Weber-Christian disease is a chronic, recurrent febrile disorder of undetermined cause with nodular panniculitis (inflammation of the subcutaneous fat) perhaps related to other mesenchymal disorders. It occurs most frequently in women and is characterized by the occurrence of crops of painful, tender, usually nonsuppurative subcutaneous nodules of greatly variable size on the buttocks, thighs, or arms and less commonly on the trunk. Early lesions suggest acute inflammation, and are elastic and relatively fixed to deeper structures, later, lesions are more discrete, firm, and movable, further regression of nodules results in a pitting appearance of the skin. The patient may be quite ill during the acute, febrile relapses. Hepatosplenomegaly may occur.

Laboratory studies are unrevealing. The diagnosis is made by excisional biopsy.

There is no effective treatment, although penicillin and the sulfonamides are reported to be of value. Corticosteroids are ineffective.

Hallahan, J. D., & T. Klein: Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease). *Ann. Int. Med.* 34-1179-1200, 1951.

Shuman, C. R.: Relapsing panniculitis (Weber-Christian disease). *Arch. Int. Med.* 87 669-81, 1951.

### SYDENHAM'S CHOREA\* (St. Vitus's Dance)

#### Essentials of Diagnosis

- Quick, jerky, involuntary, irregular movements of the face, trunk, and extremities
- Gait and speech often markedly impaired
- Irritability, restlessness and emotional instability
- Mild muscular weakness, hypotonia
- Associated rheumatic fever or residua

Differentiate from tics and habit spasms which are not related to rheumatic fever and not associated with difficulty in articulation or muscle weakness. Distinguish also from Huntington's chorea, which is hereditary, occurs in adult life, and is characterized by more rapid progression and mental deterioration.

#### General Considerations

Sydenham's chorea is seen mostly in young persons and is characterized by involuntary irregular movements, incoordination of voluntary movements, mild muscle weakness, and emotional disturbance. The disorder is usually associated with rheumatic fever and is considered to be one of its sequelae, other clinical evidence of rheumatic fever are apt to be present.

#### Clinical Findings

**A Symptoms and Signs** The patient becomes irritable, excitable, restless, and sleepless. Grimacing, clumsy movements, and stumbling frequently occur. Involuntary dysrhythmic movements of the face, trunk, and extremities occur with varying severity. These are sudden, quick, short, and jerky. Gait and speech may be affected. Voluntary movement and excitement may aggravate the involuntary movements. Affected limbs may be weak and hypotonic.

Clinical evidence of rheumatic fever or rheumatic heart disease is often present.

\*For the discussion of rheumatic fever, see p 179.

### Differential Diagnosis

Tics or habit spasms are usually manifested as facial grimacing with blinking, smacking of lips and clicking noises and there is no difficulty in articulation, no associated muscle weakness and no evidence of rheumatic fever. Huntington's chorea is a hereditary disease of adult life characterized by chorea and mental deterioration; it is progressive and usually leads to death in about 15 years.

### Treatment

Corticosteroids and corticotropin may shorten the course and ameliorate manifestations. Sedatives (such as phenobarbital) or phenothiazine tranquilizers are helpful in suppressing the involuntary movements of chorea.

### Prognosis

The acute phase of chorea usually runs a limited course with maximum symptoms 2-3 weeks after onset. Gradual recovery occurs in about 2-3 months.

Kagan B M & B Mirman Sydenham's chorea: a syndrome for differential diagnosis. *J Pediatr* 31:322-32, 1947.

### SICCA SYNDROME (Sjögren's Syndrome)

Sjögren's syndrome is a generalized connective tissue disorder of undetermined etiology with multiple systemic involvement. Dryness of the eyes, mouth and nose due to hypofunction of the lacrimal and parotid glands is characteristic. Unilateral or bilateral parotid swelling may occur. Weakness, fatigue and musculoskeletal aches and pains are common. Chronic polyarthritis, often of a rheumatoid type, may be present. The syndrome has been described in association with such a wide variety of other diseases that manifestations may be quite variable. Increased sedimentation rate, hyperglobulinemia (usually gamma globulin) and cryoglobulinemia are frequently observed. Pathologic findings in the lacrimal, salivary and submucous glands consist principally of lymphocytic and plasma cell infiltration with atrophy of the glandular tissue and diminution of secretions. Arteritis and periarteritis may occur in the viscera and lymph nodes.

Many treatment methods have been proposed but results have not been uniformly good. Local treatment of eye dryness with irrigating solution or artificial tears (methyl cellulose 0.12% in saline) instilled into the eyes every 3 hours is simple and effective. Treatment with corticotropin or the corticosteroids is warranted especially in the systemic disease but should be used with caution if corneal infection or ulceration is present.

The disease is subject to remissions and exacerbations and is usually not progressive.

Denko C W & D M Bergenstal. The sicca syndrome (Sjögren's syndrome). A study of sixteen cases. *Arch Int Med* 105:849-58, 1960.

Stolze C A & others. Keratoconjunctivitis sicca and Sjögren's syndrome. Systemic manifestations and hematologic and protein abnormalities. *Arch Int Med* 106:513-22, 1960.

### WEGENER'S SYNDROME (Wegener's Granulomatosis)

Wegener's syndrome is a generalized progressive granulomatous disorder of undetermined etiology characterized by severe sinusitis, pulmonary inflammation, multiplicity of symptoms due to generalized arteritis and terminal renal insufficiency. The disease begins with nasal, paranasal, sinus or pulmonary symptoms with chronic productive cough or hemoptysis. Fever, malaise, weakness or weight loss may be severe. Progressive destruction of the cartilage of the nose and the bony structures around the paranasal sinuses occurs later. Chemosis, papillitis and exophthalmos may occur. There may be parotitis, carditis, musculoskeletal aches and pains, prostatitis and polyneuritis. Proteinuria, hematuria and white cells and casts in the urine are evidence of marked renal involvement.

There is no known effective treatment. Corticosteroids may give temporary relief or induce temporary remissions early in the course of the disease. Death due to renal failure usually occurs within a few months.

Kinney V R, & others. Wegener's granulomatosis. *Arch Int Med* 108:264-79, 1961.

Walton E W. Giant cell granuloma of the respiratory tract (Wegener's granulomatosis). *Brit M J* 2:265-70, 1958.

## PERIODIC DISEASE

(Benign Paroxysmal Peritonitis,  
Familial Mediterranean Fever)

Periodic disease is a heredofamilial disorder of unknown pathogenesis, probably metabolic, characterized by recurrent episodes of abdominal or chest pain, fever, and leukocytosis. It is usually restricted to people of Mediterranean ancestry, primarily Armenians, Sephardic Jews, Turks, Arabs, Greeks, and Italians. The disease suggests surgical peritonitis, but the acute attacks are recurrent, self-limited, and not fatal. Diffuse amyloidosis, however, may occur in long-standing cases, and death may result from renal or cardiac failure. Acute episodes may be precipitated by emotional upsets, alcohol, or dietary indiscretion.

Recent evidence suggests that a low-fat diet (20 Gm./day) may significantly reduce the incidence of acute attacks in some patients.

Mellinkoff, S. M., Schwabe, A. D., & J. S. Lawrence. A dietary treatment for familial Mediterranean fever. *Arch. Int. Med.* 108: 80-5, 1961.

## SARCOIDOSIS (Boeck's Sarcoid)

### Essentials of Diagnosis

- Mild fever, lassitude, weakness, anorexia, and weight loss
- May involve almost any body tissue and present with lesions of the lungs, skin, bone, joints, or salivary glands and uvea (uveoparotid fever)
- Hilar adenopathy and nodular or fibrous infiltration of both lungs on chest x-ray
- Tuberculin reaction usually negative, no bacteriologic evidence of tuberculosis
- Hyperglobulinemia and hypercalcemia may occur
- Biopsy reveals noncaseating granuloma

Distinguish from tuberculosis, malignant lymphomas (especially Hodgkin's disease), collagen disorders, and primary skin, bone, and eye diseases.

### General Considerations.

Sarcoidosis is a chronic, relatively benign, noncaseating granulomatous disease of undetermined etiology which may involve any tissue of the body. Since the lungs are the second

most frequently involved site, this is an important entity in the differential diagnosis of chest diseases. Extrapulmonary lesions are diverse, but skin lesions causing atrophic scars, "punched out" lesions of the small bones of the hands and feet, uveitis, and swelling of the salivary glands are suggestive of sarcoidosis.

Although the disease may be familial, there is no evidence of communicability. Distribution is world-wide, but the incidence is highest in temperate zones, especially in the southeastern United States. The incidence in Negroes is 17 times that in whites. The usual age group is 20-40.

### Clinical Findings

**A Symptoms and Signs.** Skin lesions consist of nodules and diffuse infiltrations, especially of the face, ears, nose, and extensor surfaces. Erythema nodosum may occur. Atrophic scars may follow healing. The lymph nodes are usually involved. Enlargement of the tracheobronchial nodes may produce cough and dyspnea due to compression. Uveoparotid fever is characterized by fever, malaise, and firm, painless, persistent involvement of the parotid and other salivary glands, lacrimal gland involvement, and variable involvement of the eye with conjunctivitis, iritis, corneal and vitreous opacities, and involvement of the retina.

"Punched out" lesions of the medullary portions of the phalanges, metacarpals, and metatarsals may occur, but the periosteum is usually not involved.

Myocardial lesions may result in arrhythmias, conduction defects, and even cardiac failure.

Paralysis of the facial muscles, soft palate, and vocal cords and peripheral neuritis may be encountered.

**Pulmonary symptoms and signs** are commonly absent despite marked x-ray abnormalities. Constitutional symptoms such as night sweats, fever, and loss of weight are often minimal or absent. Cough, hemoptysis, and symptoms of pulmonary insufficiency occur late in those patients with progressive pulmonary lesions.

**B Laboratory Findings.** There are no diagnostic hematologic findings. Leukocytosis, eosinophilia (10-15%), anemia, and thrombocytopenia ("hypersplenism") occasionally appear. The sedimentation rate is usually elevated. Serum globulin is usually increased (absolute). Serum calcium and alkaline phosphatase are commonly elevated.

Tuberculin and various fungus-antigen skin tests are usually negative.

Antigen prepared from sarcoid nodes and injected intracutaneously reproduces the sarcoid tubercle locally, usually after weeks or months, in most patients with sarcoidosis (Kveim reaction). The value of this test is limited because its specificity is uncertain, antigen is difficult to prepare, and it takes a long time for the lesion to develop.

Biopsy is the definitive diagnostic procedure. The skin and lymph nodes are the most accessible sites. Even small and inconspicuous nodes may reveal typical lesions. Lymph nodes anterior to the scalenus anticus muscle are "connected" to the mediastinal nodes, and biopsy of these nodes yields a high incidence of positive results. When more superficial sites fail to produce the lesion, needle biopsy of the liver (Involved in 68% of patients) may be of value.

**C X-ray Findings** The principal finding on x-ray is hilar adenopathy, which is bilateral and striking ("potato nodes"). Paratracheal nodes also are frequently enlarged. Accentuation of perihilar markings may be noted in association with adenopathy. Pulmonary nodules are diffuse and may be small, resembling those of military tuberculosis. Hilar nodes usually regress or disappear as parenchymatous lesions appear. Progressive, advanced disease results in numerous linear and reticular densities (fibrosis). Characteristic "punched out" areas in the small bones of the hands and feet may be seen.

#### Differential Diagnosis

The most important diseases to be differentiated are tuberculosis, the collagen dis-

eases, the malignant lymphomas (especially Hodgkin's disease), and other diseases producing x-ray patterns of hilar lymphadenopathy or military pulmonary nodules. The relative clinical "silence" of sarcoidosis is an important differential feature.

#### Treatment

General supportive measures include adequate rest and nutrition. Treat constitutional or organ system symptoms symptomatically as indicated. Corticosteroid therapy may produce a prompt regression of symptoms and signs, although relapses may occur. Treatment is less effective when begun in the later stages of the illness.

#### Prognosis

Sarcoidosis is a relatively benign disease. The over-all mortality is about 5%. Pulmonary lesions usually stabilize or regress without treatment. Complications may include pulmonary tuberculosis, cardiac failure (due to actual myocardial involvement or cor pulmonale), and pulmonary insufficiency when pulmonary lesions are progressive.

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- Longcope, W.T., & D.G. Freiman: A study of sarcoidosis. *Medicine* 31:1-132, 1952.  
 Porter, G.H. Hepatic sarcoidosis. *Arch. Int. Med.* 108 483-98, 1961.  
 Sones, M., & H.L. Iarsel: Course and prognosis of sarcoidosis. *Am. J. Med.* 29 84-93, 1960.

## Bibliography.

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Kampmeier, R.H.: Collagen diseases - unanswered questions on pathogenesis and etiology. Arch. Int. Med. 106:753-85, 1960.

Milgram, F., & E. Witesky: Auto-antibodies and auto-immune diseases. J.A.M.A. 181:706-16, 1962.

Talbot, J.H., & R.M. Ferrandis: Collagen Diseases. Grune & Stratton, 1956.

Thirteenth Rheumatism Review: Rheumatism and arthritis. Ann. Int. Med. 53:149-62, 1960.

## Genitourinary Tract

Marcus A. Krupp

### NONSPECIFIC MANIFESTATIONS

#### Pain

The localization, pattern of referral and type of pain are important clues to the diagnosis of genitourinary tract disease.

A Pain caused by renal disease is usually felt as a dull ache in the "flanks" or costovertebral angle, often extending along the rib margin toward the umbilicus. Because many renal diseases do not produce sudden distention of the capsule of the kidney, absence of pain is common.

B Ureteral pain is related to obstruction and is usually acute in onset, severe and colicky, and radiates from the costovertebral angle down the course of the ureter into the scrotum or vulva and the inner thigh. The site of the obstruction may be determined by the location of the radiation of the pain: high ureteral pain is usually referred to the testicle or vulva; mid-ureteral pain to the right lower quadrant of the abdomen, and low ureteral pain to the bladder.

C Pain caused by vesical disease is felt as suprapubic discomfort or bladder neck irritation.

D Pain caused by chronic prostatic disease is uncommon.

E Pain caused by testicular inflammation or trauma is acute and severe and is occasionally referred to the costovertebral angle. Pain associated with infection of the epididymis is similar to that associated with testicular inflammation.

#### Urinary Symptoms.

Infection, inflammation, and obstruction produce symptoms associated with urination.

A Frequency, urgency, and nocturia are commonly experienced when inflammation of the urinary tract is present. Severe infection produces a constant desire to urinate even though the bladder contains only a few ml of urine. Frequency and nocturia occur when bladder capacity is diminished by disease or when the bladder cannot be emptied completely, leaving a large volume of residual urine. Nocturia associated with a large urine volume may occur with heart failure, renal insufficiency, mobilization of edema, diabetes insipidus, and ingestion of large amounts of fluid late in the evening.

B Dysuria and burning on urination are associated with infection of the bladder, prostate and urethra.

C Enuresis may be due to urinary tract disease but is most often caused by neural or psychogenic disorders.

D Urinary incontinence may be due to anatomic abnormality, physical stress, the urgency associated with infection or nervous system disease, and the dribbling associated with an overdistended flaccid bladder.

#### Characteristics of Urine.

A Cloudy urine is almost always the result of the urates or phosphates which precipitate out as urine collects in the bladder, and is usually of no significance.

B Hematuria is always of grave significance. It may be due to neoplasms, vascular accidents, infections, anomalies, stones, or trauma to the urinary tract. When blood appears in the urine only at the end of micturition, the posterior urethra or bladder neck is the most likely source of bleeding.



## DISORDERS OF THE KIDNEYS

### ACUTE GLOMERULONEPHRITIS

#### Essentials of Diagnosis

- History of preceding streptococcal infection
- Malaise, headache, anorexia, low-grade fever
- Mild generalized edema, mild hypertension, retinal hemorrhages
- Gross hematuria, protein, red cell casts, granular and hyaline casts, white cells and renal epithelial cells in urine
- Elevated antistreptolysin O titer, variable nitrogen retention

Although considered to be the hallmark of glomerulonephritis, erythrocyte casts also occur along with other abnormal elements in any disease in which glomerular inflammation and tubule damage are present, i.e. periarteritis nodosa, disseminated lupus erythematosus, subacute bacterial endocarditis, dermatomyositis, Henoch's purpura, or poisoning with chemicals toxic to the kidney

#### General Considerations

Glomerulonephritis is a disease affecting both kidneys. In most cases recovery from the acute stage is complete, but progressive involvement may destroy renal tissue and renal insufficiency results. Acute glomerulonephritis is most common in children 3-10 years of age. By far the commonest cause is an antecedent infection of the respiratory tract or of other tissues with type 12 and, occasionally, type 4 beta-hemolytic streptococci. Other infections which have been followed by glomerulonephritis include pneumococcal, staphylococcal, and bacillary infections. "Sensitivity" diseases, such as Rhus dermatitis and reactions to venom or to chemical agents, may be associated with renal disease indistinguishable from glomerulonephritis. It appears that the common mechanism in production of the renal lesion is the development of auto-sensitivity or auto-antibody reactions against renal tissue following exposure to bacterial or chemical products.

Gross examination of the involved kidney shows only punctate hemorrhages throughout the cortex. Microscopically, the primary alteration is in the glomeruli, which show pro-

liferation and swelling of the endothelial cells of the capillary tuft. The proliferation of capsular epithelium produces a thickened crescent about the tuft, and in the space between the capsule and the tuft there are collections of leukocytes, red cells, and exudate. Edema of the interstitial tissue and cloudy swelling of the tubule epithelium are common. As the disease progresses, the kidneys may enlarge. The typical histologic findings in glomerulitis are enlarging crescents which become hyalinized and converted into scar tissue and obstruct the circulation through the glomerulus. Degenerative changes occur in the tubules, with fatty degeneration and necrosis and ultimate scarring of the nephron. Arteriolar thickening and obliteration become prominent.

#### Clinical Findings

**A Symptoms and Signs** Often the disease is very mild and there may be no reason to suspect renal involvement unless the urine is examined. In severe cases, about 2 weeks following the acute streptococcal infection, the patient develops headache, malaise, mild fever, puffiness around the eyes and face, flank pain and oliguria. Hematuria is usually noted as bloody or, if the urine is acid, as 'brown' or 'coffee-colored'. Respiratory difficulty with shortness of breath may occur.

There may be moderate tachycardia and moderate to marked elevation of BP. Tenderness in the costovertebral angle area is common.

**B Laboratory Findings** The diagnosis is confirmed by examination of the urine which may be grossly bloody or coffee-colored (acid hematin) or may show only microscopic hematuria. In addition, the urine contains protein (1-3+) and casts. Hyaline and granular casts are commonly found in large numbers, but the classical sign of glomerulitis, the erythrocyte cast (blood cast) may be found only occasionally in the urinary sediment. The erythrocyte case resembles a blood clot formed in the lumen of a renal tubule, it is usually of small caliber, intensely orange or red, and under high power with proper lighting may show the mosaic pattern of the packed red cells held together by the clot of fibrin and plasma protein.

With the impairment of renal function (decrease in GFR and blood flow) and with oliguria, BUN and creatinine become elevated the levels varying with the severity of the renal lesion. The sedimentation rate is rapid. A mild normochromic anemia may be observed, in part due to overhydration. When glomerulo-

nephritis follows hemolytic streptococcal disease the antistreptolysin O titer of the serum is high (exceeding 300 Todd units)

Confirmation of diagnosis is made by examination of the urine although the history and clinical findings in typical cases leave little doubt. The finding of erythrocytes in a case is proof that erythrocytes were present in the renal tubules and did not arise from outside the renal parenchyma.

### Complications

A In severe cases signs of cardiac failure appear: cardiac enlargement, tachycardia, gallop rhythm, pulmonary passive congestion, pleural fluid, and peripheral edema.

B With severe hypertension signs of left ventricular failure often develop and the symptoms and signs of hypertensive encephalopathy may predominate: severe headache, drowsiness, muscle twitchings and convulsions, vomiting, and at times papilledema and retinal hemorrhage.

C Any infection occurring in a patient with glomerulonephritis must be regarded as a serious complication.

### Treatment

A Specific Measures. There is no specific treatment. Adrenocorticosteroids and corticotropin are of no value and may be contraindicated because they increase protein catabolism, sodium retention, and hypertension.

B General Measures. In order to avoid the undesirable effects of oliguria, the intake of water, electrolytes, and protein should be limited to quantities which can be disposed of by the poorly functioning kidney. Hospitalization is indicated if oliguria, nitrogen retention, and hypertension are present. Bed rest is of great importance and should be continued until clinical signs abate. BP and BUN should be normal for more than 1-2 weeks before activity is resumed. A guide to duration of bed rest is the urine: when protein excretion is normal and when white and epithelial cell excretion has decreased and stabilized, activity may be resumed on a graded basis. Excretion of protein and formed elements in the urine will increase with resumption of activity, but such increases should not be great. Erythrocytes may be excreted in large numbers for months, and the rate of excretion is not a good criterion for evaluating convalescence. The sedimentation rate should be near normal before unrestricted activity is allowed. If sedimentation rate increases or if urinary

findings become more pronounced with activity, return to bed rest and restricted activity are indicated for 10 days to 2 weeks before trial of activity is repeated.

In the presence of elevated BUN and oliguria, severe dietary protein restriction is indicated. If severe oliguria is present, no protein should be given. If no nitrogen retention is apparent, the diet may contain 0.5 Gm of protein/Kg. Carbohydrates should be given liberally to provide calories and to reduce the catabolism of protein and prevent starvation ketosis.

Sodium restriction varies with the degree of oliguria. In severe cases no sodium should be allowed. As recovery progresses, sodium intake can be increased.

Fluids should be restricted in keeping with the ability of the kidney to excrete urine. If restriction is not indicated, fluids can be consumed as desired. Occasionally when nausea and vomiting preclude oral consumption, fluids must be given I.V. in amounts depending upon the severity of the oliguria. Glucose must be given in sufficient quantities to spare protein and prevent ketosis.

If anemia becomes severe (hematocrit less than 30%), blood transfusions may be given. To reduce the volume given, packed red cells may be preferred to whole blood (particularly if hypertension is present and congestive failure seems imminent).

### C Treatment of Complications

1 Hypertensive encephalopathy should be treated vigorously. Sedation with barbiturates or paraldehyde may suffice in mild cases. The BP may be lowered in children or in young adults with magnesium sulfate solution (50%) given I.M. in doses of 0.2 ml/Kg; the dose may be repeated every 4 hours as needed. For I.V. use a 10% solution of magnesium sulfate may be given slowly in a dose of 100-150 mg/Kg/hour. Caution: Calcium gluconate 10% solution must be available for use as an antidote if magnesium toxicity occurs, as shown by onset of narcosis or respiratory depression.

2 Heart failure should be treated as any case of left ventricular failure with severe restriction of fluid and sodium intake, digitalization, and oxygen.

3 Infection should be promptly eradicated with appropriate antibiotics. Prophylactic penicillin for several months after the acute phase has been advocated, but its value is not proved.

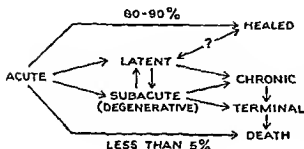
### Prognosis

Most patients with the acute disease recover completely within 1-2 years. 5-20% show

progressive renal damage. If oliguria, heart failure, or hypertensive encephalopathy is severe, death may occur during the acute attack. Even with severe disease, however, recovery is the rule, particularly in children.

Kushner, D. C., & others: Acute glomerulonephritis in the adult. *Medicine* 40 203-40, 1961.

Symposium: Glomerulonephritis. *J. Chronic Dis.* 5:1-172, 1957.



### CHRONIC GLOMERULONEPHRITIS

Progressive destruction of the kidney may continue for many years in a clinically latent or subacute form. The subacute form is similar to the latent form (see below) except that symptoms occur, i.e., malaise, mild fever, and sometimes flank pain and oliguria. Treatment is as for the acute attack. Exacerbations may appear from time to time, reflecting the stage of evolution of the disease.

### LATENT GLOMERULONEPHRITIS

#### Essentials of Diagnosis

- Clinically asymptomatic. History of acute stage may not be obtained.
- Urine shows continuing excretion of red, white, and renal epithelial cells, casts, and protein at greater than normal rate.
- Progressive decline of GFR and tubule function.

The differential diagnosis is the same as that given for acute glomerulonephritis on p. 735.

#### General Considerations.

If acute glomerulonephritis does not heal within 1-2 years, the vascular and glomerular lesions continue to progress and tubular changes occur. In the presence of smoldering, active nephritis, the patient is usually asymptomatic and the evidence of disease consists only of the excretion of abnormal urinary elements.

#### Clinical Findings

The urinary excretion of protein, red cells, white cells, epithelial cells, and casts (including erythrocyte casts, granular casts, and hyaline and waxy casts) continues at levels above normal. As renal impairment progresses, signs of renal insufficiency appear (see below).

#### Prevention

Treat intercurrent infections promptly and vigorously as indicated. Avoid unnecessary vaccinations.

#### Treatment.

Treat exacerbations as for the acute attack, nephrotic state, or incipient renal insufficiency as indicated. A normal diet, adequate for growth in childhood and adolescence, is desirable. A protein intake of 0.5-1 Gm/Kg is permissible as long as renal function is adequate to maintain normal plasma NPN. A liberal fluid intake is desirable.

Strenuous exercise may be harmful; otherwise, normal activity is permitted.

#### Prognosis.

Worsening of the urinary findings may occur with infection, trauma, or fatigue. Exacerbations may resemble the acute attack, and may be associated with intercurrent infection or trauma. Other exacerbations may be typical of the nephrotic syndrome (see below). Death in uremia is the usual outcome, but the course is variable and the patient may live a reasonably normal life for 20-30 years.

## CHRONIC RENAL INSUFFICIENCY

### Essentials of Diagnosis

- Weakness and easy fatigability, headaches, anorexia, nausea and vomiting, pruritus, polyuria
- Hypertension with secondary encephalopathy, retinal damage, heart failure
- Anemia, azotemia, and acidosis, with elevated serum potassium, phosphate, and sulfate, and decreased serum calcium and protein
- Urine specific gravity low and fixed, mild to moderate proteinuria, few red cells, white cells, and broad renal failure casts

Chronic renal insufficiency presents symptoms and signs related to the functional disability rather than to the cause of the renal damage. It is often impossible to distinguish between renal insufficiency due to chronic glomerulonephritis, pyelonephritis, malignant hypertension, diabetic nephropathy, obstructive nephropathy, and collagen disease. The presence of large kidneys characteristic of polycystic disease should serve to identify this cause of renal failure.

### General Considerations.

The pathologic picture varies with the cause of the damage to the kidney. Extensive scarring with decrease in kidney size, hyalinization of glomeruli, and obliteration of some tubules and hypertrophy and dilatation of others produce great distortion of renal architecture. The vascular changes are due to the effects of scar formation and of prolonged hypertension, with thickening of the media, fragmentation of elastic fibers, intimal thickening, and obliteration of the lumens in some areas. In diabetic nephropathy the typical glomerular lesions of intercapillary sclerosis are often distinct. The vascular lesions of periarteritis or of systemic lupus erythematosus often serve to establish these diagnoses. Obstructive uropathy presents the classical picture of hydronephrosis with compression and destruction of the renal parenchyma. Polycystic disease, multiple myeloma, amyloid disease, and other rarer causes of renal failure usually can be identified by characteristic pathologic lesions.

### Clinical Findings.

The clinical symptoms and signs of the metabolic and hypertensive components of renal failure appear insidiously and may not be noted until the effects are severe.

**A Symptoms and Signs.** Metabolic and vascular abnormalities incident to renal insufficiency produce typical symptoms and signs. The metabolic defect is due to failure of the kidney to excrete the daily load of nitrogenous waste and to excrete or conserve water and electrolytes as required to maintain balance. The result is the clinical picture of uremia with its 3 cardinal signs: azotemia, anemia, and acidosis. The uremic patient often is weak and tired, complains of anorexia and nausea and vomiting, and may have diarrhea. He is often short of breath. Pruritus is common and the excoriations may be purpuric. Pallor and a waxy appearance of the skin are often observed. Polyuria reflects the inability of the kidney tubules to absorb water, as glomerular filtration becomes greatly reduced, oliguria appears. Terminally manifestations are severe nausea, diarrhea, muscle twitching, hyperpnea, pruritus bleeding from mucous membranes, and somnolence. Urea frost on the skin and fibrinous pericarditis and pleurisy are associated with marked elevations of BUN.

Hypertension may become severe and may produce headache, convulsions, and left heart failure. Retinopathy with choked disks, hemorrhages, exudates, and severe changes of the arterioles often produce impairment of vision. Encephalopathy produces convulsions. Left heart failure is often accompanied by overt pulmonary edema.

**B Laboratory Findings.** Laboratory studies reveal the functional and chemical defects. The urine usually is dilute, contains small amounts of protein, few red cells, white cells, and epithelial cells, and a few granular and waxy casts some of which are broad in caliber (broad renal failure casts). The anemia is usually normochromic, and the hemoglobin often in the range of 6-9 Gm/100 ml. BUN and creatinine are greatly elevated. Serum sodium concentration may be slightly lower than normal, serum potassium slightly to markedly elevated, and serum calcium concentration decreased. With retention of phosphate, sulfate, and (frequently) chloride, plasma bicarbonate concentration is decreased. Retention of organic acids and loss of sodium and of bicarbonate buffer is accompanied by a decrease of plasma pH.

### Treatment.

Hypertension or heart failure should be treated as indicated.

**A. Diet and Fluids.** Limitation of protein to 0.5 Gm./Kg./day helps to reduce the nitrogen load which contributes to the azotemia.

The diet should include adequate calories. Sodium should not be restricted. Fluid intake should be sufficient to maintain an adequate urine volume, but no attempt should be made to force diuresis. Obligatory water loss may be quite high because of the large solute load (e.g., sodium and urea) which must be excreted by a reduced number of nephrons; intake must be sufficient to maintain renal function without causing excessive diuresis or edema. Caution: Water restriction for laboratory examinations or tests of renal function is hazardous.

#### B. Electrolyte Replacement:

1. Sodium supplements may be required to restore sodium losses resulting from failure of the kidney to provide  $\text{NH}_4^+$  and  $\text{H}^+$  for sodium conservation. A mixture of  $\text{NaCl}$  and  $\text{NaHCO}_3$  in equal parts, 1-2 Gm. 2-3 times daily with meals, may be required in addition to dietary sources

2. Potassium intake may have to be restricted or supplemented. Measurement of the serum potassium concentration will provide indications.

3. Calcium lactate, 4 Gm. 2-3 times daily, may be given to relieve hypocalcemic tetany. I.V. administration of calcium gluconate may be required at times

4. Serum phosphate levels may be lowered by reducing absorption of phosphate in the gastrointestinal tract with administration of aluminum hydroxide gel, 30 ml. (1 oz.) 3-4 times daily.

C. Transfusions: Transfusions of whole blood or packed red cells may be required for treatment of anemia. Iron is usually ineffective, and there is no indication that cobalt is of any use.

D. General Measures: Nausea and vomiting may be alleviated with chlorpromazine, 15-25 mg. orally or 10-20 mg. I.M. (or equivalent amounts of related compounds). The barbiturate drugs may be used for sedation as required. For convulsions it may be necessary to give barbiturates such as pentobarbital sodium, 0.25-0.5 Gm. ( $3\frac{3}{4}$ - $7\frac{1}{2}$  gr.) I.V. or I.M., or amobarbital sodium, 0.5 Gm ( $7\frac{1}{2}$  gr.) I.V. or I.M. Paraldehyde is often well tolerated orally or rectally in doses of 4-15 ml. (1-4 dr.).

#### Prognosis.

The prognosis depends upon the degree of renal failure. Intercurrent infections will hasten the downhill course.

Epstein, F. H.: Reversible uremic states.

J.A.M.A. 161:494-9, 1956.

Merrill, J. P.: The Treatment of Renal Failure, Therapeutic Principles in the Management of Acute and Chronic Uremia. Grune & Stratton, 1955

Strauss, M. B., & L. G. Raisz: Clinical Management of Renal Failure. Thomas, 1956.

## NEPHROTIC SYNDROME

### Essentials of Diagnosis

- Massive edema
- Proteinuria and cylindruria.
- Hypoproteinemia, elevated plasma cholesterol and lipids

The nephrotic syndrome (nephrosis) may be associated with a variety of renal diseases, including glomerulonephritis, collagen disease (disseminated lupus erythematosus, periarteritis nodosa, etc.), amyloid disease, thrombosis of the renal vein, diabetic nephropathy, syphilis, and reaction to toxins such as bee venom, Rhus antigen, and heavy metals. In small children, nephrosis may occur without clear evidence of any cause.

### General Considerations.

The microscopic picture is that of the underlying disease. Common to all is the fatty degeneration of tubule epithelium. Biopsy or autopsy examination of renal tissue will show glomerular and vascular changes typical of glomerulonephritis, collagen disease, amyloidosis, or intercapillary glomerulosclerosis. In so-called lipid or pure nephrosis, alterations in the glomerular basement membrane have been demonstrated with the electron microscope

### Clinical Findings.

A. Symptoms and Signs: Edema may appear insidiously and increase slowly; often it appears suddenly and accumulates rapidly. As fluid collects in the serous cavities, the abdomen becomes protuberant and the patient may complain of anorexia and become short of breath. Symptoms other than those related to the mechanical effects of edema and serous sac fluid accumulation are not remarkable.

On physical examination massive edema is apparent. Signs of hydrothorax and ascites are common. Pallor is often accentuated by the edema, and striae commonly appear in the

stretched skin of the extremities Hypertension, changes in the retina and retinal vessels, and cardiac and cerebral manifestations of hypertension may be demonstrated more often when collagen disease diabetes mellitus, or renal insufficiency is present

**B Laboratory Findings** The urine contains large amounts of protein 1-10 Gm /24 hours or more The sediment contains casts, including the characteristic fatty and waxy varieties, renal tubule cells some of which contain fatty droplets (oval fat bodies), and variable numbers of erythrocytes A mild normochromic anemia is common but anemia may be more severe if renal damage is great Nitrogen retention varies with the severity of impairment of renal function The plasma is often lipemic, and the blood cholesterol is usually greatly elevated Plasma protein is greatly reduced The albumin fraction may fall to less than 2 Gm or even below 1 Gm / 100 ml Some reduction of gamma globulin occurs in pure nephrosis, whereas in systemic lupus erythematosus the protein of the gamma fraction may be greatly elevated The serum electrolyte concentrations are often normal, although the serum sodium may be slightly low, total serum calcium may be low, in keeping with the degree of hypoalbuminemia and decrease in the protein-bound calcium moiety Urine sodium excretion is very low, and urinary aldosterone excretion elevated If renal insufficiency is present, the blood and urine findings are usually altered accordingly (see Renal Insufficiency)

#### Treatment

There is no specific treatment except for syphilis or for heavy metal poisoning Bed rest is indicated for patients with severe edema or those who have infections Infections should be treated vigorously and promptly with appropriate antibiotics Hospitalization is desirable if steroid therapy is given The diet should provide a normal protein ration (0.75-1 Gm /Kg /day) with adequate calories Sodium intake should be restricted to 0.5-1 Gm /day Potassium need not be restricted

Diuretics are often ineffective The most useful are the chlorothiazide derivatives, e.g., hydrochlorothiazide (Hydro-Diuril®), 50-100 mg every 12 hours, other chlorothiazide derivatives or chlorthalidone (Hygroton®) may be employed in comparable effective dose levels Salt-free albumin, dextran, and other oncotic agents are of little help and their effects are transient

The cortisones and corticotropin are effective agents in most cases of the nephrotic

syndrome in childhood and in adults when the syndrome is due to glomerulonephritis, systemic lupus erythematosus, or idiosyncrasy to toxin or venom Steroid therapy is of little or no value in amyloidosis or renal vein thrombosis and is contraindicated in diabetic nephropathy It is advisable not to use cortisone or hydrocortisone Give prednisolone (1-2 mg /Kg./day for children or 100-125 mg daily for adults) in divided doses orally for 10-14 days, or interrupt the dosage sooner if diuresis begins (Other steroids may be employed at comparable doses ) It may be necessary to repeat the course 2-3 times with brief intervals between courses in order to induce diuresis There may be a slight increase in edema and in proteinuria during the first few days of therapy As diuresis progresses proteinuria often diminishes When diuresis is well-established and as the patient approaches "dry" weight, give intermittent therapy as follows prednisolone, 60 mg orally daily in divided doses for 3 consecutive days of the week, no steroid being given on the succeeding 4 days At present it is considered justifiable to continue intermittent therapy for a year if the patient remains edema-free and if proteinuria is reduced to negligible amounts If exacerbations occur, therapy can be intensified Potassium supplements may be desirable during steroid therapy

**Caution:** Elevation of serum potassium, development of hypertension, and sudden severe increase in edema contraindicates continuation of steroid therapy Such complications usually arise during the first 2 weeks of continuous therapy

Corticotropin gel, 100 mg. daily I M, or corticotropin 25 mg in 5% glucose in water daily as a 12-hour I V. infusion, may be employed, but oral steroid therapy is much more simple and convenient for patient and physician

#### Prognosis

The course and prognosis depend upon the basic disease responsible for the nephrotic syndrome In about 50% of cases of childhood nephrosis the disease appears to run a rather benign course when properly treated, and to leave insignificant sequelae Of the others, most are cases of glomerulonephritis, which go inexorably into the terminal state with renal insufficiency Adults with nephrosis fare less well, because in almost all instances the fundamental disease is either glomerulonephritis, systemic lupus erythematosus, amyloidosis, renal vein thrombosis, or diabetic nephropathy In any patient a remission may be in-

duced, but the presence of hypertension or nitrogen retention are serious signs.

Derow, H.A. The nephrotic syndrome. *New England J. Med.* 258:77-82 and 124-9, 1958

Kark, R.M., & others: The nephrotic syndrome in adults, a common disorder with many causes. *Ann. Int. Med.* 49:751-74, 1958.

Lange, K., Wasserman, E., & L.B. Slobody: Prolonged intermittent steroid therapy for nephrosis in children and adults. *J.A.M.A.* 168 377-81, 1958

Muehrke, R.C., & others: Lupus nephritis a clinical and pathologic study based on renal biopsies. *Medicine* 36 1-145, 1957

### ARTERIOLAR NEPHROSCLEROSIS

Intimal thickening of the afferent arteriole of the glomerulus is the characteristic finding. Obliteration of the arteriole or severe narrowing of the lumen deprives the nephron of its blood supply and produces areas of infarction and scar formation. Obliteration of glomeruli is common. If the disease is "malignant" and rapidly progressive, points of hemorrhage are found and vascular changes, resembling an endarteritis with severe intimal thickening associated with malignant hypertension, become marked. Renal insufficiency occurs when the kidney is scarred and contracted.

The symptoms and signs are those of hypertension and renal insufficiency and, occasionally, heart failure and hypertensive encephalopathy.

Treatment is directed against hypertension and chronic renal insufficiency.

The course is progressively downhill. The patient usually succumbs to renal failure, and death is sometimes hastened by intercurrent infection.

### ACUTE RENAL FAILURE

#### Essentials of Diagnosis

- Sudden onset of oliguria, urine volume 20-200 ml /day
- Proteinuria and hematuria, isosthenuria with a specific gravity of 1.010-1.016
- Anorexia, nausea and vomiting, lethargy, elevation of BP. Signs of uremia.
- Progressive increase in serum BUN, creatinine, potassium, phosphate, sulfate, decrease in sodium, calcium,  $CO_2$
- Spontaneous recovery in a few days to 6 weeks

Patients with acute renal failure are rarely anuric, when anuria of a few days' duration occurs in a patient who appears to be in acute renal failure, it is well to investigate the possibility of urinary obstruction or to question the diagnosis. Other conditions which should be considered are glomerulonephritis, renal vascular lesions, and those causing prerenal azotemia.

#### General Considerations.

Acute renal failure is a term applied to a state of sudden cessation of renal function following a variety of insults to normal kidneys. Among the causes of acute renal failure are the following: (1) Toxic agents, e.g., carbon tetrachloride, mercury bichloride, arsenic, diethylene glycol, sulfonamides, and mushroom poisoning. (2) Traumatic shock due to severe injury, surgical shock, or myocardial infarction. (3) Tissue destruction due to crushing injury, burns, intravascular hemolysis (transurethral resection, incompatible blood transfusion). (4) Infectious diseases, e.g., leptospirosis, hemorrhagic fever, septicemia due to gram-negative bacteria with shock. (5) Severe water and electrolyte depletion. (6) Complications of pregnancy, e.g., bilateral cortical necrosis.

Return of renal function can be expected, but even with the best treatment the mortality rate is high.

Renal tubular necrosis is the characteristic finding. In some instances, after exposure to a specific toxin, the proximal tubule may be primarily damaged, and renal tubule cell disintegration and desquamation with collection of debris in the lumens of the tubules are found uniformly throughout both kidneys. In other cases, tubule cell destruction and

basement membrane disruption are scattered throughout both kidneys. In cases due to hemolysis or crushing injury, heme or myoglobin casts may be present, but it is unlikely that such casts produce tubule cell destruction. The spotty distribution of the damage is consonant with alterations in blood flow which produce ischemic necrosis. In bilateral cortical necrosis ischemic infarcts are distributed throughout both kidneys.

### Clinical Findings

The cardinal sign of acute renal failure is acute reduction of urine output following injury, surgery, a transfusion reaction, or other causes listed above. The daily volume of urine may be reduced to 20-30 ml/day or may be as high as 400-500 ml/day. After a few days to 6 weeks the daily urine volume slowly increases. Anorexia, nausea, and lethargy are common symptoms. Other symptoms and signs are related to the causative agent or event.

The course of this disease may be divided into the oliguric and diuretic phases.

**A** During the oliguric phase, the urine excretion is greatly reduced. The urine contains protein, red cells, and granular casts and the specific gravity of the urine is usually 1.010-1.016. The rate of catabolism of protein determines the rate of increase of metabolic end products in body fluids. In the presence of injury or fever, the serum DUN, creatinine, potassium, phosphate sulfate, and organic acids increase rapidly. Typically the serum sodium concentration drops to 120-130 mEq/L with a corresponding fall in serum chloride. As organic acids and phosphate accumulate, serum bicarbonate concentration decreases. Normochromic anemia is common. With prolonged oliguria signs of uremia appear with nausea, vomiting, diarrhea, neuromuscular irritability, convulsions, somnolence, and coma. Hypertension frequently develops and may be associated with retinopathy, left heart failure, and encephalopathy. During this phase of the disease, therapy modifies the clinical picture significantly. Overhydration produces signs of water intoxication with convulsions, edema, and the serious complication of pulmonary edema. Excess saline administration may produce edema and congestive failure. Failure to restrict potassium intake or to employ agents to remove potassium at the proper time may result in potassium intoxication. High extracellular potassium levels produce neuromuscular depression which progresses to paralysis and interference with the cardiac conduction sys-

tem, resulting in arrhythmias. Death may follow respiratory muscle paralysis or cardiac arrest. The ECG changes as the potassium level rises (see p. 34), first showing peaked T waves, then broadening of the QRS complex and lack of P waves, later, a biphasic ventricular complex, and, finally, cardiac arrest or ventricular fibrillation. With proper treatment, potassium intoxication is almost always reversible, and death should seldom occur because of it.

**B** Diuretic Phase. After a few days to 6 weeks of oliguria, the diuretic phase begins, signifying that the nephrons have recovered to the point that urine excretion is possible. The urine volume usually increases in increments of a few ml to 100 ml/day until 300-500 ml/day are excreted, after which the rate of increase in flow is usually more rapid. Rarely the urine volume increases rapidly during the first day or so of diuresis. Diuresis may be the result of impaired nephron function, with loss of water and electrolytes, but this is uncommon and true deficits of water, sodium, and potassium seldom occur. More often, diuresis represents an unloading of excess extracellular fluid which has accumulated during the oliguric phase, either as a result of overhydration during therapy or unusual metabolic production of water. Diuresis occurs when the total nephron function is insufficient to excrete nitrogenous metabolic products, potassium, and phosphate and the concentration of these constituents in the serum may continue to rise for several days after urine volumes exceed 1 L/day. Renal function returns slowly to normal, and blood chemical findings become normal.

### Differential Diagnosis

Because acute glomerulonephritis, ureteral obstruction due to edema at the ureterovesical junction following ureteral catheterization, ureteral obstruction by neoplasm, bilateral renal artery occlusion due to embolism or dissecting aneurysm, and, rarely, a ruptured bladder may present with symptoms and signs indistinguishable from those of tubular necrosis, appropriate diagnostic procedures should be employed as suggested by the history and by physical examination. Occasionally a profound state of dehydration may produce severe oliguria; rapid infusion of 500-1000 ml of 0.45% saline will restore blood volume temporarily to the point that glomerular filtration will increase and urine will be excreted.

### Treatment.

**A. Specific Treatment.** Immediate treatment of the cause of oliguria is essential.



1. Shock - Vigorous measures to restore normal BP levels are mandatory. In order to overcome renal ischemia (see p. 2), Csution: When it becomes apparent that tubular necrosis has occurred, the volume of fluids administered must be sharply curtailed; if vasopressor drugs are required, they must be given in the limited amount of fluid permitted.

2. Transfusion reaction - See p. 272.

3. Obstruction of ureters - Cystoscopy and catheterization of ureters may be necessary.

4. Heavy metal poisoning - Dimercaprol (BAL) may be of use in mercury or arsenic poisoning, although by the time the renal lesion is apparent it may be too late.

#### B. General Measures.

1. Oliguric phase - The objectives of therapy are to maintain normal body fluid volume and electrolyte concentration, reduce tissue catabolism to a minimum, and prevent infection until healing occurs.

(1) Bed rest "Reverse isolation" to protect the patient from exposure to hospital infections.

(2) Fluids: Restrict fluids to a basic ration of 400 ml./day for the average adult. Additional fluid may be given to replace unusual losses due to vomiting, diarrhea, sweating, etc. The metabolism of fat, carbohydrate, and protein provides water of combustion, and catabolism of tissues provides intracellular water. These sources must be included in calculations of water balance, thus leaving only a small ration to be provided as "intake."

(3) Diet. No protein may be given. Glucose, 100-200 Gm./day, should be given to prevent ketosis and to reduce protein catabolism. Although fat may be given as butter or as an emulsion for oral or I.V. use, it is usually better to permit the patient to fulfill caloric needs from his own fat deposits.

The fluid and glucose may be given orally or I.V. When administered I.V. as a 20-50% glucose solution, the 400 ml. of fluid should be given continuously through the 24-hour period through an I.V. catheter threaded into a large vein to reduce the likelihood of thrombosis. Vitamin B complex and vitamin C should be provided.

(4) Electrolyte replacement. Replace preexisting deficits. Otherwise, electrolyte therapy is not necessary unless clear-cut losses are demonstrable, as in vomiting, diarrhea, etc. Note: Potassium must not be administered unless proved deficits exist, and then only with caution.

(5) Observations: Daily records of fluid intake and output are essential; an indwelling

catheter is usually required to permit accurate measurement of urine output. Weight should be recorded daily whenever possible. Because the patient is consuming his own tissues, he should lose about 0.5 Kg./day. If he fails to lose weight, he is receiving too much fluid. Frequent (often daily) measurements of serum electrolytes (especially potassium) and creatinine are essential.

(6) Infection. Treat vigorously with appropriate antibiotics, bearing in mind that the drug may not be excreted. "Reverse isolation" is a useful protective measure.

(7) Congestive heart failure - See p. 216.

(8) Anemia: A hematocrit of less than 30% is an indication for cautious transfusion with a small volume of packed fresh red blood cells.

(9) Potassium intoxication - See p. 34.

(10) Uremia. The artificial kidney and peritoneal dialysis are effective, but require expert management in a well-equipped hospital.

(11) Convulsions and encephalopathy. Give paraldehyde rectally. Barbiturates should be restricted to pentobarbital sodium or amobarbital sodium, which are metabolized by the liver. Chlorpromazine and promazine are also useful.

2. Diuretic phase - Unless water and electrolyte deficits clearly exist, no attempt should be made to "keep up" with the diuresis; collections of excess water and electrolyte are usually being excreted. Fluid and diet intake can be liberalized as diuresis progresses until a normal daily intake is reached. Protein restriction should be continued until serum BUN and creatinine levels are declining. Infection is still a hazard. Occasionally diuresis will be accompanied by sodium retention, hypernatremia, and hyperchloremia associated with confusion, neuromuscular irritability, and coma. When this happens, water and glucose must be given in sufficient quantities to correct hypernatremia.

#### Prognosis

If severe complications of trauma and infection are not present, skillful treatment often will tide the patient over the period of oliguria until spontaneous healing occurs. Death may occur as a result of water intoxication, congestive heart failure, acute pulmonary edema, potassium intoxication, and encephalopathy. With recovery there is little residual impairment of renal function.

Doolan, P.D., & others: An evaluation of intermittent peritoneal lavage. *Am. J. Med.* 26:831-44, 1959.

Franklin S S , & J P Merrill Acute renal failure New England J Med 262 711-8 and 761-7, 1960

Swann R C & J P Merrill The clinical course of acute renal failure Medicine 32 215-92 1953

Symposium The clinical application of the artificial kidney Arch Int Med 102 871 921, 1958

## CONGENITAL ANOMALIES OF THE KIDNEYS

### 1 FUNCTIONAL OR INTRINSIC TUBULAR DEFECTS

#### Defects of Water Absorption (Renal Diabetes Insipidus)

Symptoms are related to inability to reabsorb water i.e. polyuria and polydipsia. The urine volume approaches 12 L/day and the specific gravity is low.

There is no response to antidiuretic hormone (vasopressin).

There is no treatment.

#### Defects of Glucose Absorption (Renal Glycosuria)

This results from an abnormally low ability to reabsorb glucose so that glycosuria is present when blood glucose levels are normal. Ketosis is not present. The glucose tolerance response is usually normal. In some instances renal glycosuria may precede the onset of true diabetes mellitus.

There is no treatment for renal glycosuria.

#### Defects of Glucose & Phosphate Absorption (Glycosuric Rickets)

The symptoms and signs are those of rickets or osteomalacia with weakness, pain or discomfort of the legs and spine, and tetany. The bones become deformed with bowing of the weight bearing long bones, kyphoscoliosis, and in children signs of rickets. X-ray shows markedly decreased density of the bone with pseudofracture lines and other deformities. Nephrocalcinosis may occur with excessive phosphaturia and renal insufficiency may follow. Urinary calcium and phosphorus are increased and glycosuria is present. Serum glucose is normal, serum calcium is normal or low, serum phosphorus is low and serum alkaline phosphatase is elevated.

Treatment consists of giving large doses of vitamin D and calcium supplementation of the diet.

#### Defects of Phosphorus & Calcium Absorption

**A Vitamin D-resistant Rickets** Excessive loss of phosphorus and calcium result in rickets or osteomalacia which respond poorly to vitamin D therapy. Treatment consists of giving large doses of vitamin D and calcium supplementation of the diet.

**B Pseudohypoparathyroidism** As a result of excessive reabsorption of phosphorus, hyperphosphatemia and hypocalcemia occur. Symptoms include muscle cramps, fatigue, weakness, tetany, and mental retardation. The signs are those of hypocalcemia. In addition, the patients are short, round-faced, and characteristically have short fourth and fifth metacarpal and metatarsal bones. The serum phosphorus is high, serum calcium low, and serum alkaline phosphatase normal. There is no response to parathyroid hormone.

Vitamin D therapy and calcium supplementation may prevent tetany.

**C Idiopathic Hypercalcemia** Decreased reabsorption of calcium predisposes to the formation of renal calculi. Serum calcium and phosphorus are normal. Urine calcium excretion is high, urine phosphorus excretion is low.

There is no treatment.

#### Defects of Hydrogen Ion Secretion & Bicarbonate Reabsorption (Renal Tubular Acidosis)

Failure to secrete hydrogen ion and to form ammonium ion results in loss of fixed base, sodium, potassium, and calcium. There is also a high rate of excretion of phosphate. Vomiting, poor growth, and symptoms and signs of chronic metabolic acidosis are accompanied by weakness due to potassium deficit and the bone discomfort due to osteomalacia. The urine is alkaline and contains larger than normal quantities of sodium, potassium, calcium, and phosphate. Nephrocalcinosis may be present. The blood chemical findings are those of metabolic acidosis (low  $\text{HCO}_3^-$  or  $\text{CO}_2$ ) with hyperchloremia, low serum calcium and phosphorus, low serum potassium, and occasionally low serum sodium.

Treatment consists of replacing deficits and increasing the intake of sodium, potassium, calcium, and phosphorus. Sodium and potassium should be given as bicarbonate or citrate. Additional vitamin D may be required.

#### Defects of Amino Acid Reabsorption

**A Congenital Cystinuria** Increased excretion of cystine results in the formation of

cystine urinary tract calculi. Nonopaque stones should be examined chemically to provide a specific diagnosis.

Maintain the urine pH above 7.0 by giving sodium bicarbonate and sodium citrate. In refractory cases a low-methionine (cystine precursor) diet may be necessary.

**B. Aminoaciduria:** Many amino acids may be poorly absorbed, resulting in unusual losses. Failure to thrive and the presence of other tubular deficits suggest the diagnosis.

There is no treatment.

**C. Hepatolenticular Degeneration:** In this congenital familial disease, aminoaciduria is associated with cirrhosis of the liver and neurologic manifestations (see p. 455). Hepatomegaly, evidence of impaired liver function, spasticity, sthosis, emotional disturbances, and Kayser-Fleischer rings around the cornea constitute a unique syndrome. There is a decrease in synthesis of ceruloplasmin with a deficit of plasma ceruloplasmin and an increase in free copper which may be etiologically specific.

Give penicillamine to chelate and remove excess copper. Edathamil (Versenate<sup>®</sup>, EDTA) may also be used to remove copper.

#### Multiple Defects of Tubular Function (De Toni-Fanconi-Debre Syndrome).

Aminoaciduria, phosphaturia, glycosuria, and a variable degree of renal tubular scidosis characterize this syndrome. Osteomalacia is a prominent clinical feature, other clinical and laboratory manifestations are associated with specific tubular defects described separately above.

Treatment consists of replacing cation deficits, especially potassium and calcium, and giving vitamin D, a high-calcium diet, and continued supplements of sodium and potassium.

#### Excess Potassium Secretion (Potassium "Wastage" Syndrome).

Excessive secretion or loss of potassium may occur in 4 situations: (1) Chronic renal insufficiency with diminished  $H^+$  secretion; (2) Renal tubular scidosis and the De Toni-Fanconi syndrome, with cation loss resulting from diminished  $H^+$  and  $NH_4^+$  secretion; (3) Aldosteronism and hyperadrenocorticism; (4) Tubular secretion of potassium, the cause of which is yet unknown. Hypokalemia indicates that the deficit is severe. Muscle weakness, metabolic alkalosis, and polyuria with dilute urine are signs attributable to hypokalemia.

Treatment consists of correcting the primary disease and giving supplementary potassium.

**Reiman, A.S., & N.G. Levinsky:** Kidney disease acquired tubular disorders (with special reference to disturbances of concentrations and dilution and of acid-base regulation). *Ann. Rev. Med.* 12:93-110, 1961.

**Renal tubular scidosis** (leading article). *Lancet* 1:82-5, 1961.

**Stanbury, J.B., Wyngaarden, J.B., & D.S. Fredrickson:** *The Metabolic Basis of Inherited Disease*. Blackiston, 1960.

## 2. STRUCTURAL DEFECTS

Congenital structural anomalies of the kidney must always be considered in any patient with hypertension, pyelonephritis, or renal insufficiency. The manifestations of structural renal abnormalities are related to the superimposed disease, but management and prognosis are modified by the structural anomaly.

### Polycystic Kidneys.

Polycystic kidney disease is familial and often involves not only the kidney but the liver and pancreas as well.

The formation of cysts in the cortex of the kidney is thought to result from failure of union of the collecting tubules and convoluted tubules of some nephrons. New cysts do not form, but those present enlarge and, by pressure, cause destruction of adjacent tissue. Cysts may be found in the liver and pancreas. The incidence of cerebral vessel aneurysms is higher than normal.

Cases of polycystic disease are discovered during the investigation of hypertension, by diagnostic study in patients presenting with pyelonephritis or hematuria, or by investigating the families of patients with polycystic disease. At times, flank pain due to hemorrhage into a cyst will call attention to a kidney disorder. Otherwise the symptoms and signs are those commonly seen in hypertension or renal insufficiency. On physical examination the enlarged, irregular kidneys are easily palpable.

The urine may contain leukocytes and red cells. With bleeding into the cysts there may also be bleeding into the urinary tract. The blood chemical findings reflect the degree of renal insufficiency. X-ray examination shows

the enlarged kidneys, and urography demonstrates the classical elongated calyces and renal pelvis stretched over the surface of the cysts

No specific therapy is available, and surgical interference is contraindicated. Hypertension, infection, and uremia are treated in the conventional manner.

Although the disease may become symptomatic in childhood or early adult life, it usually is discovered in the fourth and fifth decades. Unless fatal complications of hypertension or urinary tract infection are present, uremia develops very slowly and patients live longer than with other causes of renal insufficiency

#### Renal Agenesis.

Occasionally one kidney, usually the left, is congenitally absent. The remaining kidney is hypertrophied. The incidence of pyelonephritis appears to be greater in those so afflicted. Before performing a nephrectomy for any reason, it is mandatory to prove the patient has a second kidney

#### Horseshoe Kidney.

A band of renal tissue or of fibrous tissue may join the 2 kidneys. Associated abnormalities of the ureterocalyceal system predispose to pyelonephritis

#### Ectopic Kidney.

The kidney may occupy a site in the pelvis and the ureter may be shorter than normal. Infection is more frequent in such kidney

#### Nephroptosis

Unusual mobility of the kidney permits it to move from its normal position to a lower one. Only when ureteral kinking or poor drainage can be clearly shown to produce symptoms or to encourage persistence of infection is surgical intervention justified.

Dalgaard, O.Z.: Bilateral polycystic disease of the kidneys, a follow-up of two hundred and eighty-four patients and their families. *Acta med. scandinav.* 158, Suppl. 328, 1957.

Glenn, J.F.: Analysis of 51 patients with horseshoe kidney. *New England J. Med.* 281:684-7, 1959.

## INFECTIONS OF THE URINARY TRACT

### PYELONEPHRITIS

Pyelonephritis is an infectious disease so common and so serious in its long-term effects that meticulous attention must be paid to the details of diagnosis and treatment. Urinary tract infection is undoubtedly the commonest cause of chronic renal disease in both sexes, it is the commonest cause of "renal hypertension" in women and a frequent cause in men. Because the chronic form of the disease is associated with few symptoms, the diagnosis is often not established until signs of renal insufficiency or hypertension appear. Resistance to treatment is remarkable, and relapses are frequent

### 1. ACUTE PYELONEPHRITIS

#### Essentials of Diagnosis

- Sudden onset of chills and fever with urinary frequency and urgency and burning on urination, pain and tenderness in the costovertebral angle over the kidneys
- Headache, prostration, nausea and vomiting
- Urine contains pus (pyuria), few to many red cells, granular and white cell casts, small to moderate amounts of protein, bacteria
- Leukocytosis, rapid sedimentation rate
- Occasionally bacteremia

Acute pyelonephritis must be differentiated from acute causes of abdominal pain as well as from basal pneumonia. Acute pancreatitis must also be considered. The presence of pus and bacteria in the urine will usually confirm the diagnosis of pyelonephritis

#### General Considerations.

Acute urinary tract infections may be confined to the bladder, but more often the infection involves the ureters and kidneys as well. In many cases, anatomic defects of the genitourinary tract produce obstruction or stasis which favor invasion and persistence of pathogenic organisms. The organisms most

frequently found are the gram-negative bacilli, i.e., *Escherichia coli*, *Aerobacter aerogenes*, *Paracolon species*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, and *salmonellae*, and the gram-positive cocci, i.e., streptococci (enterococci) and staphylococci. In acute urinary tract infections the causative organism is present in great numbers, ranging from 10,000 to hundreds of millions of bacteria per milliliter of urine.

Predisposing factors are of importance. In young people infection is much more frequently encountered in the female. In the older age groups, infection is more common in the male since urinary tract obstruction is more frequent. Pregnancy, diabetes mellitus, metabolic disorders with nephrolithiasis, obstructive uropathy, neurogenic bladder, and genitourinary instrumentation are all associated with a high incidence of urinary tract infection.

Pathologic examination shows inflammation of the bladder, ureters, and kidney pelvis, with edema, intense capillary congestion, patchy ulceration and submucosal hemorrhage in the more severe cases. On section the kidney shows linear streaks of yellow, which represent purulent involvement of the tubules and interstitial tissues of the pyramids and medulla, often extending into the cortex. Microscopically, interstitial tissue suppuration with patchy necrosis and pus-filled tubules are prominent. Although the glomeruli are not directly involved, interstitial inflammation of the glomeruli may be intense.

### Clinical Findings

**A. Symptoms and Signs.** Symptoms are those of acute infection, with chills, fever, prostration, and headache. Local urinary tract symptoms include urinary urgency and frequency, dysuria, tenesmus, pain and tenderness in the flanks over the kidneys, and backache. Nausea, vomiting, and occasionally diarrhea are common. There may be few signs of infection other than dysuria and frequency. Physical examination usually reveals little except tenderness over the kidneys and the signs of fever and prostration.

**B. Laboratory Findings.** The WBC is usually 14,000-20,000/cu mm, with an increase of polymorphonuclear neutrophils (including band forms). The sedimentation rate is very rapid. The urine contains pus with clumps of polymorphonuclear cells, granular and leukocyte casts, some red cells and epithelial cells, shreds of mucus, protein, and at times acetone.

Cultures of the urine reveal multitudes of bacteria; blood cultures are occasionally positive as well. Examination of the urine is extremely important, for only if the organism is identified can therapy be properly directed. A gram-stained smear of the sediment obtained from 5-10 ml of urine will show identifiable bacteria when these are present in concentrations of 10,000 or more/ml of urine. A WBC can be made on uncentrifuged urine in a counting chamber, if the count exceeds 2 white cells/cu mm (i.e., 2 cells per 9 squares), pyuria is present. Urine cultures should be performed either on fresh catheterized specimens or on fresh midstream specimens after proper cleansing of the urethral meatus and, in the female, exclusion of labial and vaginal contamination. Quantitative cultures should be done with 0.1 ml of undiluted urine and 0.1 ml of 1:100 dilution. Each colony on the plate inoculated with the undiluted urine represents 10 bacteria/ml, and each colony on the plate inoculated with the 1:100 dilution represents 1000 bacteria/ml. Higher dilutions may be cultured if counts over 100,000 are expected. If bacteria are seen on a gram-stained smear or if the quantitative culture exceeds 10,000 organisms/ml of urine, the diagnosis of urinary tract infection is confirmed. Counts of 1000 or less can be considered to represent contamination, counts between 1000 and 10,000 are indeterminate, although urinary tract infection is unlikely in these instances.

### Treatment.

**A. Specific Measures.** Give specific anti-infective drugs chosen on the basis of cultures and sensitivity tests. The sulfonamides, nitrofurantoin, the tetracyclines, mandelic acid, and methionine should be employed in doses sufficient to produce adequate levels in the renal tissues and urine. Chloramphenicol, colistimethate (Colistin®), neomycin, and polymyxin should be reserved for cases refractory to other agents.

Prolonged and continuous antimicrobial therapy is required to eradicate infectious organisms. Follow-up urine cultures should be taken to prove absence of infection.

When the acute phase has passed, diagnostic studies should be undertaken to demonstrate any anatomic or metabolic defect: x-ray of the abdomen, urograms, cystoscopy, ureteral urine culture, and cystograms and cystourethrograms to determine reflux of urine into the ureters, and appropriate tests for coexisting metabolic disease.

Anatomic abnormalities which cause obstruction, stasis, or reflux should be corrected if possible.

**B General Measures** Place the patient at bed rest on a regular diet as tolerated and force fluids to maintain a high urine output. I.V. administration of fluids is often required. Give antipyretics and analgesics as indicated. Treat associated disease such as diabetes mellitus.

### Prognosis

In the absence of anatomic defects of the urinary tract, appropriate antimicrobial therapy will usually result in cure. Recurrent or continued infection produces renal damage with ultimate development of renal insufficiency or hypertension.

See references under Chronic Pyelonephritis opposite.

## 2 CHRONIC PYELONEPHRITIS

### Essentials of Diagnosis

- Asymptomatic except for exacerbations of symptoms of acute urinary tract infection.
- End stages of chronic infection are characterized by symptoms and signs of renal insufficiency, uremia, and hypertension.
- Urine may be unremarkable or may contain leukocytes, bacteria, and protein.

### General Considerations

Chronic pyelonephritis is often unsuspected unless a history of urinary tract infection or of unexplained and peculiar gastrointestinal symptoms is elicited. When hypertension is present, the possibility of pyelonephritis must always be entertained. Since the disease is often unilateral and nephrectomy may be curative if the function of the other kidney is normal. Before renal insufficiency develops, proper treatment may delay or prevent the serious sequelae of continuing infection.

Because of variations in the degree of involvement, one kidney may be larger than the other. Severely damaged kidneys are greatly contracted, and may consist mostly of scar tissue and remnants of renal tissue enclosed in a thickened capsule. Areas of chronic or acute interstitial inflammation may be present. Terminally the clinical features are indistinguishable from the end stage of glomerulonephritis or nephrosclerosis.

### Clinical Findings

There are none unless clear-cut exacerbations of more acute urinary tract infection occur. The late manifestations are those of renal insufficiency or of hypertension.

**Treatment** (See also the discussions of acute pyelonephritis, uremia, and hypertension.)

Treat infection with appropriate antimicrobial drugs. If renal function is reduced, mandelic acid and methionine must not be used because the kidneys are no longer able to regulate electrolyte and  $H^+$  homeostasis. Anatomic defects which favor infection should be corrected surgically if possible.

### Prognosis

Unless the infection is eradicated, one or both kidneys will be damaged so severely that irremediable hypertension or renal insufficiency will result. However, the course of the disease may be protracted over many years and with careful management these patients may lead a reasonably comfortable life even when renal reserve is limited.

Kllemann C R, Hewitt W L, & L B Guze  
Pyelonephritis. *Medicine* 39:3-116, 1960.  
Quinn E L & E H Kasa (editors). *Biology of Pyelonephritis*. Henry Ford Hospital International Symposium. Little, Brown, 1960.

## LOWER URINARY TRACT INFECTION

Because the urinary tract is a continuous duct with relatively ineffective separation of the ureterocalyceal system from the urinary bladder, it is hazardous to assume that an isolated infection of the bladder exists.

The principles of diagnosis and management of urinary tract infection stated above (see Pyelonephritis, p. 746) apply to the so-called lower urinary tract infections or cystitis also. Anatomic and neurogenic defects and metabolic diseases such as diabetes mellitus and those conducive to stone formation must be searched for and corrected. Cultures must be made and suitable antimicrobial agents employed.

It is important to remember that a urinary tract infection is not an infection in the urine alone but in the tissues of the urinary tract as well.

## TUBERCULOSIS OF THE URINARY TRACT

### Essentials of Diagnosis

- Early symptoms are usually those of vesical infection, including burning on urination, frequency, and nocturia
- Malaise, fatigability, fever, night sweats
- There are usually few signs. The kidney or kidneys may be enlarged, the epididymides may be enlarged and indurated, a scrotal sinus may be present
- Urine contains "pus without organisms" on a Gram or methylene blue stain, red cells, and usually protein
- Culture or guinea pig inoculation confirms the presence of *Mycobacterium tuberculosis*
- Urograms show "moth-eaten" appearance of calyces, abscess cavities, and varying degrees of kidney destruction

The "sterile" pyuria of chronic pyelonephritis and chronic nonspecific urethritis and cystitis may mimic tuberculous infection. Culture and biopsy should serve to distinguish tuberculosis from these.

### General Considerations.

Hematogenous dissemination of tubercle bacilli from foci in the lung or lymph nodes is the usual source of tuberculosis of the kidney, rarely does the infection originate in the genital tract. The genital organs may become infected by hematogenous spread or secondary to kidney infection. The prostate, seminal vesicles, epididymides, and, rarely, the testes may be infected. The fallopian tubes are more frequently involved than the ovaries and uterus.

The kidney and ureter may show little gross change. Caseous nodules in the renal parenchyma and abscess formation with destruction of tissue and fibrosis often produce extensive damage. Calcification in the lesions is common. The ureter and calyces are thickened, and stenosis may occur with total destruction of functioning renal tissue above. The bladder shows mucosal inflammation and submucosal tubercles which become necrotic and form ulcers. Fibrosis of the bladder wall occurs late or upon healing. Tubercles with caseous necrosis and calcification are found in the genital organs. Microscopically, typical tubercles are found and demonstration of the tubercle bacilli in the lesions is usually easily accomplished.

The search for tuberculosis elsewhere in the body must be complete whenever urinary tract tuberculosis is found.

### Clinical Findings

**A Symptoms and Signs** Symptoms are not characteristic or specific. Manifestations of chronic infection with malaise, fever, fatigability, and night sweats may be present. Kidney and ureter infection is usually silent. Bladder infection produces frequency, burning on urination, nocturia, and, occasionally, tenesmus. If bleeding occurs with clot formation, ureteral or vesical colic may occur. Gross hematuria is fairly common. Genital involvement becomes apparent as enlargement of the epididymis occurs or as a sinus tract forms.

Examination may reveal only costovertebral angle tenderness and the alterations in the genital tract organs available to palpation.

**B Laboratory Findings** The urine contains "pus without bacteria," red cells, and usually protein. Culture for tubercle bacilli and guinea pig inoculation confirm the diagnosis. If renal damage is extensive, signs of renal insufficiency can be demonstrated: elevated BUN or NPN and serum electrolyte abnormalities characteristic of uremia. A mild anemia usually is present, and the sedimentation rate is rapid.

**C X-ray and Cystoscopic Findings** Excretory urograms will reveal the moth-eaten appearance of the involved calyces or the obliteration of calyces, stenosis of calyces, abscess cavities, ureteral thickening and stenosis, and the nonfunctioning kidney (auto-nephrectomy). Calcification of involved tissues is common. Thorough cystoscopic examination is required to determine the extent of bladder wall infection and to provide biopsy material if needed.

### Treatment.

**A Medical Treatment** If renal infection is unilateral but gross necrosis is not evident, or if renal infection is bilateral, place the patient at bed rest and give antituberculosis therapy. Antituberculosis therapy as follows must be continued for at least 2 years: Amino-salicylic acid (PAS) 8-12 Gm orally daily, isoniazid (INH), 3-5 mg/Kg orally daily, and streptomycin 1 Gm I.M. twice a week. Pyridoxine, 50 mg/day, may be given to combat the vitamin B<sub>6</sub> depletion effect of isoniazid.

**B Surgical Plus Medical Treatment** If renal infection is unilateral and the involved

kidney is severely damaged with areas of necrosis or if stenosis of the calyces or ureter is present combined medical treatment (as above) plus nephrectomy is indicated. If one kidney is severely involved by a caseous hydronephrosis or is bleeding severely, nephrectomy (and medical therapy) may be necessary even though the other kidney is infected.

Combined therapy may be required also for advanced genital organ or vesical tuberculosis.

**Prognosis**

The prognosis varies with the extent of renal involvement and damage to renal function. Antimicrobial therapy has improved the outlook remarkably. Anatomic defects resulting from scar and healing or from stenosis of the ureter with hydronephrosis may delay or preclude cure.

Vesical or genital tuberculosis responds less well than does uncomplicated renal infection.

Lattimer, J. K., & R. J. Kohen. Renal tuberculosis. *Am J Med* 17:533-9, 1954.  
Ross, J. C., Gow, J. G., & C. A. St. Hill. The treatment of genito-urinary tuberculosis: a review of 240 patients. *Lancet* 1:116-9, 1955.

**ACUTE PROSTATITIS**

Acute prostatitis may represent an exacerbation of chronic prostatitis (perhaps due to instrumentation) or may occur as a result of hematogenous infection from a distant source or local extension of a urethral infection. Urinary tract infection and urinary retention often occur with acute prostatitis. The pathologic changes are those characteristic of infection and inflammation, occasionally with abscess formation.

The manifestations are those of infection and local inflammation. Characteristic symptoms are low-grade to high fever, low back or perineal pain, and urinary bladder irritability with dysuria, frequency, nocturia, urgency, and, at times, inability to void because of urethral obstruction. The physical finding of an exquisitely tender, swollen prostate gland confirms the diagnosis. Variable leukocytosis, pyuria, and bacteriuria are present, and often a purulent urethral discharge. Culture is required to identify the specific organism.

Acute prostatitis must be differentiated from urinary tract infection.

Antibiotics should be selected on the basis of cultures and sensitivity tests. Instrumentation of the urethra is contraindicated. Drainage of an abscess requires perineal exposure of the gland. Bed rest is essential. Analgesics, sitz baths, and bladder sedatives should be given as necessary for discomfort. A high fluid intake is helpful.

Acute prostatic infection is usually readily controlled with appropriate antibiotics. Inadequate treatment may result in a chronic residual infection.

Bruce, A. W., & M. Fox. Acute infections of the prostate gland. *Brit J Urol* 31:302-5, 1959.

**CHRONIC PROSTATITIS**

Chronic prostatitis may persist after an acute infection has subsided. The gland is often firmer than normal as fibrosis takes the place of inflamed tissue. The ducts contain pus and the ductal mucosa degenerates. Seminal vesical inflammation and, in many cases, epididymitis are present.

Although chronic prostatitis is usually asymptomatic, there may be complaints of fullness and pain in the perineum or low back. Urethral discharge may occur. Symptoms of cystitis, epididymitis, or partial urethral obstruction may be present. The prostate is usually enlarged and boggy, with indurated areas. Crepitation may be elicited on palpation if stones are present. The prostatic and seminal fluid will be purulent. The urethral discharge will reveal the offending bacterial organism or trichomonads. Careful examination of the prostatic secretion is important. Calcium stones of the prostate may be seen on x-ray.

Antibiotic therapy with appropriate agents should be employed. Prostatic massage may be helpful and should be repeated every 1-3 weeks. Vigorous therapy of epididymitis or complicating urinary tract infection is mandatory. Urethral obstruction, epididymitis, and urinary tract infection are serious complications. Otherwise, chronic prostatitis is not likely to be harmful, but eradication of infection should be attempted to prevent complications which, in turn, sustain chronic disease.



## URINARY STONES

Urinary stones and calcification in the kidney may be associated with metabolic disease, may be secondary to infection in the urinary tract, or may be idiopathic. The incidence of urinary tract calculus is higher in men.

### NEPHROCALCINOSIS

#### Essentials of Diagnosis

- Asymptomatic, or symptoms of primary disease producing hypercalciuria.
- Physical signs of the primary disease
- Anemia is common
- Blood chemical findings of primary disease plus variable degrees of renal insufficiency.

Differentiate from renal calculi, renal tuberculosis, and medullary sponge kidney.

#### General Considerations.

Chronic hypercalciuria and hyperphosphaturia may result in precipitation of calcium salts in the renal parenchyma. The commonest causes are hyperparathyroidism, hyper-vitaminosis D (particularly with associated high-calcium intake), and excess calcium and alkali intake. Chronic pyelonephritis predisposes to nephrocalcinosis. Other causes include acute osteoporosis following immobilization, sarcoidosis, renal tubular acidosis, the De Toni-Fanconi syndrome, and destruction of bone by metastatic carcinoma.

#### Clinical Findings.

The symptoms, signs, and laboratory findings are those of the primary disease. The diagnosis is usually established by x-ray demonstration of calcium deposits in the kidney, which appear as minute calcific densities with linear streaks in the region of the renal papillae. True renal stones may be present as well.

#### Treatment.

Specific treatment is directed at the primary disorder. Particular attention is directed to treatment of urinary tract infection and renal insufficiency. When renal tubular acidosis or the De Toni-Fanconi defect is present, it is

essential to maintain a high fluid intake, to replace cation deficit, and to alkalize the urine with sodium bicarbonate, 4-5 Gm. q. i. d., or sodium or potassium citrate, 50% solution, 4-8 ml. q. i. d. Even with adequate treatment, the prognosis is poor.

Epstein, F.H.: Calcium and the kidney. *J. Chron. Dis.* 11:255, 1960.

Mortensen, J.D., & A.H. Baggenstoss: Nephrocalcinosis: a review. *Am. J. Clin. Path.* 24: 45-63, 1954.

Mortensen, J.D., & J.L. Emmett: Nephrocalcinosis: a collective and clinicopathologic study. *J. Urol.* 71:398-406, 1954.

### RENAL STONE

#### Essentials of Diagnosis

- Often asymptomatic
- Symptoms of obstruction of calyx or ureteropelvic junction, with flank pain and colic
- Nausea, vomiting, abdominal distention
- Hematuria
- Chills and fever and bladder irritability if infection is present.

Differentiate from acute pyelonephritis, renal tumor, renal tuberculosis, and infarction of the kidney.

#### Etiology.

A Excessive Excretion of Relatively Insoluble Urinary Constituents.

##### 1 Calcium -

- (1) Idiopathic hypercalciuria
- (2) High-calcium intake
- (3) High vitamin D intake increases dietary calcium absorption, which increases the load of calcium excreted by the kidney
- (4) Primary hyperparathyroidism produces increased excretion of calcium and phosphate in the urine. Serum calcium is high and serum phosphorus low.

(5) Prolonged immobilization (due to spinal cord injury, poliomyelitis, fractures) and destructive bone disease increase the loss of calcium from bone, resulting in hypercalciuria

(6) Renal tubular acidosis is associated with inability to conserve cations, including calcium.

2. Oxalate - About half of urinary stones are composed of calcium oxalate.

(1) High oxalate intake (cabbage, spinach, tomatoes, rhubarb, chocolate)

(2) Congenital or familial oxaluria

3 Cystine - Hereditary cystinuria

4 Uric acid -

(1) Gout Stone may form spontaneously or due to treatment with uricosuric agents

(2) Therapy of neoplastic disease with agents which cause rapid tissue breakdown resulting in increased excretion of uric acid

B Physical Changes in the Urine

1 Increased concentration of urinary constituents when fluid intake is low

2 Urinary pH - Inorganic salts are ordinarily less soluble at high pH Organic substances are least soluble at low pH

C Nucleus (Nidus) for Stone Formation

1 Organic material, particularly bits of necrotic tissue or blood clot, may serve as a nucleus for stone formation

2 Clumps of bacteria, particularly when infection is accompanied by stasis or obstruction

## General Considerations

The location and size of the stone and the presence or absence of obstruction determine the changes which occur in the kidney and calyceal system. The pathologic changes may be modified by ischemia due to pressure or by infection.

## Clinical Findings

A Symptoms and Signs Often a stone trapped in a calyx or in the renal pelvis is asymptomatic. If a stone produces obstruction in a calyx or at the ureteropelvic junction dull flank pain or even colic may occur. Hematuria and symptoms of accompanying infection may be present. Nausea and vomiting may suggest enteric disease. Flank tenderness and abdominal distention may be the only physical findings.

B Laboratory Findings Leukocytosis may be present if there is an infection. The urine may contain red cells, white cells and protein. Pus and bacteria occur with infection. Crystals in the urine may provide a clue to the type of stone, e.g., uric acid or cystine. Chemical abnormalities in the blood and urine will confirm the diagnosis of the primary metabolic disease (e.g., hyperparathyroidism, gout, cystinuria, renal tubular acidosis).

C X-ray Findings The x-ray examination will reveal radiopaque stones, delineate kidney size, demonstrate bone lesions of parathyroid disease, gout, and metastatic neoplasms. Excretory and retrograde urograms help to delineate the site and degree of obstruction.

## Complications

Infection and hydronephrosis are complications which may destroy renal tissue.

## Prevention of Further Stone Formation

A Obtain a stone for analysis whenever possible.

B Treat predisposing disease, e.g., surgical removal of parathyroid tumor or hyperplastic parathyroid glands, treat gout, cystinuria and renal tubular acidosis as indicated.

C For calcium phosphate stones maintain a low urinary pH by giving sodium acid phosphate 0.6 Gm. cranberry juice 200 ml, or methionine 3 Gm. 3-4 times daily, and by placing the patient on an acid-ash diet. The patient should check urine pH with nitrazine paper. Reduce phosphate absorption with aluminum hydroxide gel, 120-180 ml (4-6 oz.) daily.

D For uric acid and cystine stone formation maintain a high urinary pH by giving sodium citrate, 50% solution 4-8 ml (1-2 dr.) q.i.d. or oftener and by placing the patient on an alkaline-ash diet. The patient should check urine pH with nitrazine paper.

## Treatment

Small stones may be passed. They do no harm if infection is not present. Larger stones may require surgical removal if obstruction is present or renal function threatened. Nephrectomy may be necessary.

Force fluids to maintain a dilute urine and restrict calcium intake.

Combat infection with appropriate antibiotics.

## Prognosis

If obstruction can be prevented and infection eradicated the prognosis is good.

## URETERAL STONE

### Essentials of Diagnosis

- Obstruction of ureter produces severe colic with radiation of pain to regions determined by position of the stone in the ureter
- Gastrointestinal symptoms common
- Urine usually contains red cells
- May be asymptomatic
- Exacerbations of infection when obstruction occurs

Differentiate from clots due to hemorrhage, from tumor, acute pyelonephritis, and acute cholecystitis

### General Considerations.

Ureteral stones are formed in the kidney but produce symptoms as they pass down the ureter

### Clinical Findings

**A Symptoms and Signs** The pain of ureteral colic is intense. The patient may be in mild shock, with cold, moist skin. There is marked tenderness in the costovertebral angle. Abdominal and back muscle spasm may be present. Referred areas of hyperesthesia can often be demonstrated.

**B Laboratory Findings** As for renal stone

**C X-ray and Instrumental Examination** X-rays may show the stone lodged in the ureter or at the ureterovesical junction. Nonopaque stones can be demonstrated by excretory urograms, which reveal the site of obstruction and the dilated ureteropelvic system above it. Because of the danger of infection, cystoscopy and ureteral catheterization should be avoided unless retrograde urography is essential.

### Prevention

As for renal stone

### Treatment.

**A Specific Measures** Most stones will pass spontaneously if spasm of the ureter is relieved and fluids are forced. Surgical removal may be necessary if the stone is large or if infection is present which does not respond readily to treatment.

**B General Measures** Morphine or other opiates should be given in doses adequate to control pain. Morphine sulfate, 8 mg ( $\frac{1}{8}$  gr) (or equivalent dosage of other drugs),

may be given I.V. and repeated in 5-10 minutes if necessary. Thereafter, subcut administration is usually adequate. Atropine sulfate 0.8 mg ( $\frac{1}{80}$  gr) subcut, or methantheline bromide (Banthine®), 0.1 Gm I.V., may be used as antispasmodics.

### Prognosis

If obstruction and infection can be treated successfully, the outlook is excellent.

## VESICAL STONE

### Essentials of Diagnosis

- Bladder irritability with dysuria, urgency and frequency
- Interruption of urinary stream as stone occludes urethra
- Hematuria
- Pyuria

Differentiate from pedunculated vesical tumor

### General Considerations

Vesical stones occur most commonly when there is residual urine infected with urea-splitting organisms (e.g. *Proteus*, *staphylococci*). Thus bladder stones are associated with urinary stasis due to bladder neck or urethral obstruction, diverticula, neurogenic bladder, and cystocele. Foreign bodies in the bladder act as foci for stone formation. Ulceration and bladder inflammation predispose to stone formation.

Most vesical stones are composed of calcium phosphate, calcium oxalate, or ammonium magnesium phosphate.

### Clinical Findings

**A Symptoms and Signs** Symptoms of chronic urinary obstruction or stasis and infection are usually present. Dysuria, frequency and urgency, and interruption of the urinary stream (causing pain in the penis) when the stone occludes the urethra are common complaints. Physical findings include prostatic enlargement, evidence of distended (neurogenic) bladder, a cystocele. Occasionally the stone may be palpable.

**B Laboratory Findings** The urine shows signs of infection and contains red cells.

**C X-ray and Cystoscopic Examination** X-ray examination shows the calcified stone, and urograms show the bladder abnormalities.

and upper urinary tract dilatation due to long standing back pressure. Direct cystoscopic examination may be necessary for final diagnosis.

#### Treatment

**A Specific Measures** Surgical removal of the stone is indicated either by transurethral manipulation or cystotomy.

**B General Measures** Give analgesics as required and treat infection with appropriate antibiotics. Anti infective measures are usually of little value until the stone is removed and obstruction is relieved.

#### Prognosis

If obstruction and infection can be prevented the prognosis is excellent.

- Butt A J (editor) Treatment of Urinary Lithiasis Thomas 1960  
 Melick R A & P H Henneman Clinical and laboratory studies of 207 consecutive patients in a kidney stone clinic New England J Med 259 307 14 1958  
 Vermuelen C W Miller G H & J B Sawyer Some nonsurgical aspects of urolithiasis M Clin North America 39 281 95 1955

## TUMORS OF THE GENITOURINARY TRACT

### ADENOCARCINOMA OF KIDNEY (Hypernephroma)

#### Essentials of Diagnosis

- Painless gross hematuria
- Fever
- Enlarged kidney may be palpable
- Evidence of metastases

Differentiate from hydronephrosis, polycystic kidneys, renal cyst and renal tuberculosis.

#### General Considerations

The commonest malignant tumor of the kidney is adenocarcinoma which occurs more frequently in males. This tumor metastasizes early to the lungs, liver and long bones. Adenocarcinoma of the kidney apparently arises from renal tubule cells or adenomas.

It invades blood vessels early. Microscopically the cells resemble renal tubule cells arranged in cords and varying patterns.

#### Clinical Findings

**A Symptoms and Signs** Gross hematuria is the most frequent sign. Fever is often the only symptom. A flank mass may be palpable. Vena cava occlusion may produce characteristic patterns of collateral circulation and edema of the legs. Gross hematuria is almost always present.

**B Laboratory Findings** Occasionally polycythemia may develop. Anemia is more commonly found. Urinary exfoliative cytology may confirm the diagnosis.

**C X ray examination** may show an enlarged kidney. Metastatic lesions of bone and lung may be revealed. Excretory or retrograde urography (or both) must be employed to establish the presence of a renal tumor.

#### Treatment

Nephrectomy is indicated if no metastases are present. Even when metastases are present, nephrectomy may be indicated if bleeding or pain is intractable.

X ray irradiation of metastases may be of value although the lesions are usually fairly radioresistant. Isolated single pulmonary metastases can occasionally be removed surgically.

#### Prognosis

The course is variable. Some patients may not develop metastases for 10-15 years after removal of the primary tumor. About 25% of patients live more than 5 years.

Berger L & M W Sinkoff Systemic manifestations of hypernephroma: a review of 273 cases. Am J Med 22 791 6 1957

Flocks R H & M C Kadesky Malignant neoplasms of the kidney: an analysis of 353 patients followed five years or more. J Urol 79 196 201 1958

### EMBRYOMA OF THE KIDNEY (Wilms' Tumor)

Embryoma is a highly malignant mixed tumor which occurs almost exclusively in children under 6 years of age. It metastasizes early to the lungs, liver and brain.

Weight loss and anorexia are the most common signs. Pain occurs rarely. The enlarged kidney is usually easily palpable. Metastases produce an enlarged liver. Hypertension is common. Anemia may be present. The urine is not remarkable. X-ray examination demonstrates the tumor and metastases in the lung. Excretory urograms and gastrointestinal examination help to determine the size of the tumor.

Wilms's tumor must be differentiated from hydronephrosis, polycystic kidney disease, and neuroblastoma of the adrenal medulla.

Treatment consists of nephrectomy followed by local irradiation and irradiation of metastases. Antitumor chemotherapy may be of value.

Cure can be achieved if metastases have not occurred before nephrectomy.

Kinzell, R. C., & others: Wilms's tumor: a review of 47 cases. A discussion of the findings and results of treatment of histologically proved cases in a 15-year period. *J. A. M. A.* 174:1925-9, 1960.

## TUMORS OF THE RENAL PELVIS & URETER

Epithelial tumors of the renal pelvis and ureter are relatively rare. They are usually papillary and tend to metastasize along the urinary tract. Epidermoid tumors are highly malignant and metastasize early.

Painless hematuria is the most common complaint. Colic occurs with obstruction due to blood clot or tumor. Tenderness in the flank may be found. Anemia due to blood loss occurs. The urine contains red cells and clots; white cells and bacteria are present when infection is superimposed. Urography should reveal the filling defect in the pelvis and show obstruction and dilatation of the ureter. At cystoscopy, the bleeding from the involved ureter may be seen and satellite tumors identified. Exfoliative cytologic studies should be done.

Radical removal of the kidney, the involved ureter, and the perireteral portion of the bladder should be done unless metastases are extensive.

Irradiation of metastases is usually of little value.

The prognosis depends upon the type of tumor. With anaplastic neoplasms, death usually occurs within 2 years.

## TUMORS OF THE BLADDER

### Essentials of Diagnosis.

- Hematuria.
- Suprapubic pain and bladder symptoms associated with infection.
- Visualization of tumor at cystoscopy.

Hematuria and pain can be produced by other tumors of the urinary tract, urinary calculi, renal tuberculosis, acute cystitis, or acute nephritis.

### General Considerations.

Bladder tumors are second to prostatic tumors in frequency. At least 75% of bladder tumors occur in males over the age of 50. Tumors often arise at the base of the bladder and involve ureteral orifices and the bladder neck. Papillary tumors and transitional cell and epidermoid carcinomas are frequent, adenocarcinomas and sarcomas are rare. Metastases involve regional lymph nodes, bone, liver, and lungs.

### Clinical Findings.

A. Symptoms and Signs: Hematuria is the commonest symptom. Cystitis with frequency, urgency, and dysuria is a frequent complication. With encroachment on the bladder neck, the urinary stream is diminished. Suprapubic pain occurs as the tumor extends beyond the bladder. Obstruction of the ureters produces hydronephrosis, frequently accompanied by renal infection and in which case the signs of urinary tract infection may be present. Physical examination is not remarkable. The bladder tumor may be palpable on bimanual (abdomino-rectal or abdomino-vaginal) examination. Exfoliative cytology is often diagnostic.

B. Laboratory Findings: Anemia is common. The urine contains red cells, white cells, and bacteria.

C. X-ray and Instrumental Examination: Excretory urography may reveal ureteral obstruction. Cystograms usually show the tumor. Cystoscopy and biopsy confirm the diagnosis.

### Treatment.

A. Specific Measures: Transurethral resection may be adequate to remove local and superficial tumors. Cystectomy with uretero-sigmoidostomy or another urinary diversion procedure is required for invasive tumors. Radiation therapy may be useful for more anaplastic tumors.

**B General Measures** Urinary tract infection should be controlled with appropriate antibiotics. Diversion of urine to the bowel often produces hyperchloremic acidosis and azotemia which can be controlled only by frequently emptying the bowel and by meticulous control of electrolyte intake.

### Prognosis

There is a tendency toward recurrence and increasing malignancy. With infiltrating carcinomas the outlook is poor even with radical resection.

Wallace, D. M. (editor). Tumors of the bladder. Monographs on neoplastic disease. Vol. 11. Williams & Wilkins, 1959.

## BENIGN PROSTATIC HYPERPLASIA

### Essentials of Diagnosis

- Prostatism, hesitancy and straining to initiate micturition, reduced force and caliber of the urinary stream, nocturia.
- Acute urinary retention.
- Enlarged prostate.
- Uremia follows prolonged obstruction.

Obstruction may be caused by urethral stricture, vesical stone, bladder tumor, neurogenic bladder, or carcinoma of prostate.

### General Considerations

Hyperplasia of the prostatic periurethral glands produces enlargement of the prostate and urethral obstruction.

### Clinical Findings

**A Symptoms and Signs** The symptoms of prostatism increase in severity as the degree of urethral obstruction increases. On rectal examination the enlarged prostate can be palpated. Infection commonly occurs with stasis and retention of residual urine. Hematuria may occur. Uremia may result from prolonged back pressure and severe bilateral hydronephrosis. Residual urine can be measured by post-voiding catheterization.

**B X-ray and Cystoscopic Examination** Excretory urograms reveal the complications of back pressure: ureteral dilatation and hydronephrosis and post-voiding urinary retention. Cystoscopy will reveal the enlargement of the prostate and the secondary bladder wall changes such as trabeculation, diverticula,

inflammation due to infection, and vesical stone.

### Treatment

**A Specific Measures** Relieve acute urinary retention by catheterization. Maintain catheter drainage if the degree of obstruction is severe. Surgery is usually necessary. There are various indications for each of the 4 approaches: transurethral resection or prostatectomy by suprapubic, retropubic, and perineal procedures.

**B General Measures** Treat infection of the urinary tract with appropriate antibiotics.

### Prognosis

Surgical resection will relieve symptoms. Surgical mortality is low.

## CARCINOMA OF THE PROSTATE

### Essentials of Diagnosis

- Prostatism.
- Hard consistency of the prostate.
- Metastases to bone produce pain, particularly in the low back.
- Anemia. Elevated serum acid phosphatase with extension of the cancer beyond the prostatic capsule.

Differentiate from benign prostatic hyperplasia, urethral stricture, vesical stone, bladder tumor, and neurogenic bladder.

### General Considerations

Cancer of the prostate is rare before the age of 60. It metastasizes early to the bones of the pelvis and locally may produce urethral obstruction with subsequent renal damage. The growth of the tumor is increased by androgens and inhibited by estrogens. The prostatic tissue is rich in acid phosphatase, and when cancer has extended beyond the prostate to the periprostatic tissue or to bone, the serum acid phosphatase is increased. When bone metastases occur, the serum alkaline phosphatase is increased. The serum acid phosphatase concentration thus provides a good index of the extent and growth of the tumor, and serum alkaline phosphatase signifies its extension to bone.

### Clinical Findings

**A Symptoms and Signs** Obstructive symptoms similar to those of benign prostatic

hyperplasia are common. Rectal examination reveals a stone-hard prostate which is often nodular and fixed. Low back pain occurs with metastases to the bones of the pelvis and spine. Pathologic fractures may occur at the sites of metastases. Obstruction may produce renal damage and the symptoms and signs of renal insufficiency.

**B Laboratory Findings** Anemia may be extreme if bone marrow is replaced by tumor. The urine may show evidence of infection. Serum acid phosphatase is increased when metastases have occurred, and serum alkaline phosphatase may be elevated as new bone is formed at the site of metastases. Biopsy by transurethral resection or by needle aspiration through the perineum establishes the diagnosis.

**C X-ray Findings** X-ray examination of the bones of the pelvis, spine, ribs, and skull will reveal the typical osteoblastic metastases. Excretory urograms delineate changes secondary to urethral obstruction and the back pressure of urine retention.

## Treatment.

Cure may be obtained before metastasis has occurred by radical resection of the prostate, including the seminal vesicles and a portion of the bladder neck. Palliative therapy includes transurethral resection to relieve obstruction. Antiandrogen therapy slows the rate of growth and extension of the cancer. Orchiectomy and diethylstilbestrol, 5 mg. daily (or equivalent of another estrogen), or estrogen therapy alone, are often effective. Irradiation of bone metastases may afford relief.

The effectiveness of therapy can be judged by clinical response and by periodic measurements of the serum acid and alkaline phosphatase.

## Prognosis

Palliative therapy is often not effective for long. Most patients die within 3 years, a few survive for 5-10 years.

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- Pool, T. L., & G. J. Thompson. Conservative treatment of carcinoma of the prostate. *J. A. M. A.* 160:833-7, 1958.  
Whitmore, W. F. Hormonal therapy in prostatic cancer. *Am. J. Med.* 21:687-713, 1956.

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Colby, F. H. Essential Urology, 4th ed. Williams & Wilkins, 1961.  
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- and Function. Churchill, 1958.  
Hamm, F. C., & S. R. Weinberg. Urology in Medical Practice, 2nd ed. Lippincott, 1962.  
Lippman, R. W. Urine and the Urinary Sediment, a Practical Manual and Atlas, 2nd ed. Thomas, 1962.  
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## Diseases Due to Physical Agents

Milton J. Chatton & John L. Wilson

### DISORDERS DUE TO COLD

Exposure to cold produces immediate localized vasoconstriction followed by generalized vasoconstriction. When the skin temperature falls to 25°C (77°F), tissue metabolism is slowed but the demand for oxygen is greater than the slowed circulation can supply and the area becomes cyanotic. At 15°C (59°F), tissue metabolism is markedly decreased and the dissociation of oxyhemoglobin is reduced, which gives a pink, well-oxygenated appearance to the skin. Tissue survival at this temperature is slight. Tissue death may be caused by ischemia and thromboses in the smaller vessels or by actual freezing. Freezing (frostbite) does not occur until the skin temperature drops to -4 to -10°C (25 to 14°F) or even lower, depending on such factors as wind, mobility, venous stasis, malnutrition, and occlusive arterial disease.

#### Prevention of Cold Injury

"Keep warm, keep moving, and keep dry." Wear warm, dry clothing, preferably several layers, with a windproof outer garment. Remove wet clothing, socks, and shoes as soon as possible and replace with dry ones. Extra socks, mittens, and insoles should always be carried in a pack when in cold or icy areas. Avoid cramped positions, constricting clothing, and prolonged dependency of the feet. Exercise arms, legs, fingers, and toes to maintain circulation. Avoid wet and muddy ground and keep sheltered from wind. Maintain good nutrition and skin cleanliness. Tobacco and alcohol should be avoided when the danger of frostbite is present.

### CHILBLAIN (PERNIO)

Chilblains are red, itching skin lesions, usually on the extremities, caused by exposure to cold without actual freezing of the tissues. They may be associated with edema or blistering and are aggravated by warmth. With continued exposure, ulcerative or hemorrhagic lesions may appear and progress to scarring, fibrosis, and atrophy.

Treatment consists of elevating the affected part slightly and allowing it to warm gradually at room temperature. Do not rub or massage injured tissues or apply ice or heat. Protect the area from trauma and secondary infection.

Lynn, R. B. Chilblains. Surg Gynae. & Obst  
99 720-6, 1954

### FROSTBITE

Frostbite is injury of the superficial tissues due to freezing. It may be divided into three grades of severity: (1) First degree freezing without blistering or peeling, (2) second degree freezing with blistering or peeling, and (3) third degree freezing with death of skin and perhaps the deeper tissues.

In mild cases the symptoms are numbness, prickling, and itching. With increasing severity there may be paresthesia and stiffness. Thawing causes tenderness and burning pain. The skin is white or yellow, loses its elasticity, and becomes immobile. Edema, blisters, necrosis, and gangrene may appear.

#### Treatment.

##### A. Immediate Treatment

1. Rewarming - The value of rewarming has not been conclusively established since patients are seldom seen while the tissues are still frozen. Superficial frostbite (frostnip) of extremities in the field can be treated by firm,



steady pressure (without rubbing), by placing fingers in the armpits, and in the case of the toes or heels, by removing footwear, drying feet, rewarming, and covering with adequate dry socks or other protective footwear. Rapid thawing at temperatures slightly above body heat may significantly decrease tissue necrosis. It has been suggested that rewarming is best accomplished by immersing the frozen portion of the body for several minutes in water heated to 44°C (112°F) (not warmer). After thawing has occurred and the part has returned to normal temperature, discontinue external heat. Do not permit the patient to walk on thawed feet or toes since this is likely to cause serious tissue destruction. Never permit rewarming by exercise or thawing by rubbing with snow or ice-water.

2 Protection of the part - Avoid trauma e.g., pressure or friction. Physical therapy is contraindicated in the early stage. Keep the patient at bed rest with the affected parts elevated and uncovered at room temperature. Do not apply casts, dressings, or bandages.

3 Anti-infective measures - Prevention of infection after the rewarming process is of great importance. Local infections may be treated with mild soaks (see p. 93), with or without anti-infective agents. Prophylactic penicillin injections are probably advisable if ulceration has occurred, antitetanus immunization is warranted.

4 Anticoagulants - If anticoagulants are to be of value they must be given within 24 hours after thawing. Rapid-acting heparin sodium (see p. 256 for dosage) to prolong the clotting time for about one week may be useful in preventing secondary thromboses in surrounding areas.

5 Follow-up Care. Gentle progressive physical therapy to promote circulation is important as the healing process occurs. Buerger's exercises should be instituted as soon as tolerated (see p. 243).

C Surgery. In general, surgical intervention is to be avoided. Amputation should not be considered until it is established that the tissues are dead. Tissue necrosis (even with black eschar formation) may be quite superficial and the underlying skin may heal well spontaneously.

Edwards, E A., & R W Leeper. Frostbite: an analysis of 71 cases. *J A M A* 149: 1199-1205, 1952.

Washburn, B. Frostbite: what it is, how to prevent it, and emergency treatment. *New England J Med* 266: 974-90, 1962.

## IMMERSION SYNDROME (Immersion Foot or Trench Foot)

Immersion foot (or hand) is caused by prolonged immersion in cool or cold water or mud. The affected parts are first cold and anesthetic, become hot with intense burning and shooting pains during the hyperemic period, and pale or cyanotic with diminished pulsations during the vasospastic period, later followed by blistering, swelling, redness, heat, ecchymoses, hemorrhage or gangrene and secondary complications such as lymphangitis, cellulitis and thrombophlebitis.

Treatment is best instituted during stage of reactive hyperemia. Immediate treatment consists of protecting the extremities from trauma and secondary infection and gradual rewarming by exposure to cool air (not ice or heat). Do not massage or moisten the skin or immerse the part in water. Bed rest is required until all ulcers have healed. Keep the affected parts elevated to aid in removal of edema fluid and protect pressure sites (e.g., heels) with pillows. Penicillin should be used if infection develops.

Later treatment is as for Buerger's disease (see p. 245).

Ungley, C C. The immersion foot syndrome. *Advances Surg* 1: 269-336, 1949.

## DISORDERS DUE TO HEAT

Exposure to excessive heat results in prompt peripheral vasodilatation, increased cardiac output and sweating. The resultant circulatory instability may lead to syncope if the patient remains erect and immobile, but muscular activity usually prevents syncope.

Fluid loss through sweating may amount to 3-4 L/hour with heavy work at high temperatures. The salt content of sweat increases to 0.2-0.5% with rising temperatures.

Acclimatization usually results after 8-10 days of exposure to high temperatures, but even a fully acclimatized person may suffer a disorder in the event of excessive fatigue, severe infection, alcoholic intoxication or failure to maintain hydration, salt intake or caloric intake. Breakdown may be due to circulatory failure or failure of the sweating mechanism. Cessation of sweating may indicate impending stroke or collapse.

**Prevention of Disorders Due to Heat.**

Avoid unnecessary exposure to heat and maintain adequate fluid and salt intake, using 0.1% saline as drinking water or salt tablets and water. Activity should be increased slowly until acclimatized. Clothing should be loose-fitting (preferably white) and permeable to moisture. Avoid alcoholic indulgence, excessive fatigue, and infections. Maintain good nutrition.

### HEAT STROKE (Sunstroke)

Heat stroke is a rare disorder characterized by sudden loss of consciousness and by failure of the heat-regulating mechanism as manifested by high fever and cessation of sweating. There may be premonitory headache, dizziness, nausea, convulsions, and visual disturbances. The skin is hot, flushed and dry, the pulse rapid, irregular, and weak and the BP is low. The rectal temperature may be as high as 108-112°F (42-44°C). Hydration and salt content of the body are normal.

Treatment is aimed first at reducing high temperature. Place the patient in a shady, cool place and remove his clothing. Cool him by fanning after sprinkling with water. As soon as possible, immerse him in cold water or use ice packs or ice water enemas. Do not lower the rectal temperature below 102°F (39°C.) too rapidly. Massage the extremities to maintain circulation. Sedatives are contraindicated unless the patient is in convulsions since this further disturbs the heat-regulating mechanism. Give physiologic saline solution, 1000 ml. very slowly I.V.

Patients with heat stroke should avoid immediate re-exposure to heat. Hypersensitivity to high temperature may remain for a considerable time. It may be necessary to move to a more moderate climate in order to prevent a further episode of heat stroke.

- Baxter, C R., & P E Teschan. Atypical heat stroke with hypernatremia, acute renal failure, and fulminating potassium intoxication. *Arch Int Med* 101:1040-50, 1958.
- Malamud, N., Haymaker, W., & R P Custer. Heat stroke, a clinicopathologic study of 125 fatal cases. *Mil Surgeon* 99:397-449, 1946.

### HEAT EXHAUSTION (Heat Prostration)

Heat exhaustion is due to inadequacy or collapse of the peripheral circulation secondary to salt depletion and dehydration. The symptoms are weakness, dizziness, stupor, and headache, with or without muscle cramps. The skin is cool and pale and there is profuse perspiration, oliguria, tachycardia and hypotension. Mental confusion and muscular incoordination may occur. Laboratory studies reveal hemoconcentration and salt depletion.

Place the patient at rest in a cool place, elevate feet and massage his legs. Give sodium chloride 0.1% solution, by mouth, or physiologic saline, 1000-2000 ml I.V. Treat shock when present (see p. 2). Avoid immediate re-exposure to heat.

### HEAT CRAMPS

Heat cramps are painful spasms of the involuntary muscles of the abdomen and extremities due primarily to salt depletion. The skin is moist and cool, and muscle twitches may be present. The temperature is normal or only slightly increased. Laboratory studies reveal hemoconcentration and low serum sodium.

Sodium chloride, 1 Gm. (15 gr.) every 1/2-1 hour with large amounts of water, or physiologic saline solution by mouth or I.V. usually relieves the attack promptly. Place the patient in a cool place and massage sore muscles gently. Rest should be continued for 1-3 days depending upon the severity of the attack.

### BURNS

Burns may be caused by a wide variety of agents, including flame, hot water, steam, chemicals, electricity, or radiation. The general principles of management are the same in all types.

#### Evaluation of the Patient.

A General Condition of the Patient. Treatment and prognosis depend upon the severity of the burns, the time elapsed before proper treatment, the age of the patient (out-

look is less favorable in elderly patients), and whether or not there are complicating medical disorders (e.g., diabetes, cardiovascular, and renal disease). Inhalation of smoke and fumes can cause serious respiratory obstruction or pulmonary edema. Shock may appear quite early, and if not treated promptly can progress rapidly to stupor, coma, and death. Shock should be anticipated in all patients with burns involving more than 15-20% of the body surface area.

#### B Depth or Degree of Burns

- 1 First degree - Erythema without blistering
- 2 Second degree - Erythema with blistering
- 3 Third degree - Destruction of full thickness of skin and often of deeper tissues

C. Estimate of Extent of Burn. The amount of body surface burned and the depth of the burn determine the fluid losses. The "rule of nines" is a useful means of estimating the percentage of total body surface involved by second or third degree burns of specific skin areas (see p. 30). Each upper extremity and the head are considered to represent 9% of the total surface area, each lower extremity, 18%, the anterior surface of the trunk, 18%, and the posterior surface of the trunk, 18%. Second or third degree burns of over 20% of total body surface usually cause marked fluid loss which results in burn shock. The mortality rate in second or third degree burns of 50% of total body surface is about 50%, second and third degree burns of over 75% of total body surface are almost always fatal.

D Clinical Observations. Vital signs (pulse, temperature, respiration, and BP) should be recorded hourly for the first 24 hours and at appropriate intervals thereafter. The general status of the patient should be carefully evaluated frequently, observe especially for evidence of shock, infection or respiratory embarrassment. Fluid intake and output must be carefully recorded. Hematocrit should be determined repeatedly in severe burns. Blood should be typed and cross-matched and the urine examined for blood and hemoglobin.

E Symptoms of Fluid Deficiency in Burns. Very close attention to clinical signs and symptoms is of great importance, particularly during the first 24 hours after the burn has occurred. Excessive thirst, vomiting, restlessness, disorientation, and mania - together with

increase in pulse rate, decrease in BP, collapsed veins and oliguria - are indications that fluid losses have exceeded the rate of fluid replacement. The urinary output should ideally be 30-50 ml/hour. However, if the rate of urinary excretion is below 30 ml/hour it is important to rule out acute renal insufficiency before increasing the fluid intake. The diagnosis of acute renal insufficiency is outlined on p. 741.

Urine volumes greater than 100 ml/hour indicate that too much fluid has been given, but after 48 hours the urinary output is completely unreliable as a guide to therapy. In part this is because the nitrogenous wastes released from the burned tissues act as diuretics, in addition electrolyte deficits may force compensatory elimination of water, as in the developing phase of the low-salt syndrome. Under these conditions therapy is guided almost exclusively by clinical signs and symptoms, giving sufficient fluid to maintain normal turgor of the unburned skin, fullness of the veins and moisture of the oral mucosa. The quantities of fluid required may be surprisingly large. However, care must be taken to avoid overhydration and water intoxication, which produce edema of the unburned tissues and in severe cases coma and death.

F Parenteral replacement therapy is discussed on p. 30.

For I.V. use a balanced electrolyte mixture such as lactated Ringer's injection, which contains a mixture of sodium chloride and sodium lactate. Is preferred to normal saline. Treatment of shock requires the use of blood and either plasma or a plasma expander such as dextran (Expandex®) etc.)

G Oral Replacement Solutions. Fluid and electrolyte replacement by the oral route can frequently be employed, alone or as a supplement to the I.V. route. For oral administration a well-cooled solution containing 3 Gm/L of sodium chloride and 1.5 Gm/L of sodium bicarbonate may be used. This mixture contains 70 mEq/L of sodium, it is hypotonic and therefore better tolerated than isotonic solutions.

H Criteria for Use of Whole Blood or of Plasma. When the hematocrit is high, whole blood cannot be used unless large quantities of electrolyte-containing solutions are given simultaneously. If the hematocrit is below 60% and is decreasing, whole blood may then be used, on the other hand, a hematocrit above 60% which is increasing indicates a primary need for electrolyte-containing solutions, plasma or a plasma expander, or both.

Blood will probably be needed for patients whose burns are deep and extensive or who show signs of peripheral circulatory collapse. If at the same time the hematocrit is low and electrolytes alone have failed to bring about clinical improvement:

**I Use of Potassium** The excretion of potassium is high during the acute phase of burns and may remain high for several weeks. A poor food intake at this time will prevent adequate replacement of dietary potassium. Beginning on the third or fourth day of treatment, give potassium chloride 3-4 Gm (45-60 gr) orally in fruit juice or broth 3 times a day until a full normal diet is taken.

#### J Additional Guides to Fluid Therapy

**1 Water tolerance test** - When it is suspected that low urine output is due to inadequate intake rather than to renal failure, give 1000 ml of 5% dextrose in water I V in one hour. A sharp rise in urine output during or immediately after the infusion suggests that the kidneys are functioning satisfactorily and that fluid intake should be increased.

**2 Phenol red (PSP) test** If hydration seems adequate but urinary output is low, administer PSP 1 ml I V. Excretion of more than 10% of the dye in one-half hour indicates that acute renal failure is not present and that oliguria is due to inadequate fluid intake.

### EARLY CARE OF THE BURN WOUND

#### First Aid.

**A First degree burns usually require no treatment**

**B Minor second degree burns may be washed carefully with bland soap and water and dressed with sterile petrolatum and gauze and a pressure bandage. Change the dressing after 5-8 days**

**C Severe burns should not be washed, greased, powdered, or painted with medications of any kind. Wrap the burned area in clean towels or sheets and transfer the patient to a hospital immediately**

#### Surgical Procedures In Severe Burns

##### A General Measures

**1 Control pain** which is usually severe with morphine sulfate 10-15 mg ( $\frac{1}{4}$ - $\frac{1}{2}$  gr) I V or I M, or other narcotic (see p 7). General anesthesia is rarely necessary for the

initial cleansing and dressing of severe burns if a narcotic is used and procedures are done gently.

**2 Draw blood immediately for PCV, CBC and blood grouping and cross matching**

**3 Start an infusion of lactated Ringer's injection or physiologic saline solution through the needle used for drawing blood or, preferably through an I V catheter**

**4 Place an indwelling catheter in the bladder if the patient is unable to void freely**

##### B Treatment of Burned Area

**1 Aseptic technic is essential** Wear cap, mask, sterile gown and gloves when dressing burns. Sterile linen, instruments and dressings are required.

**2 Cleanse burn and surrounding area with bland or hexachlorophene soap and sterile warm water. Wash gently with gauze sponges. Remove grease or oil with ether or benzene**

**3 Debride carefully** Remove only loose and necrotic tissue. Puncture blebs aseptically and leave them in place as protective coverings.

**4 Apply petrolatum gauze and a pressure dressing** Place a single layer of petrolatum (or Xeroform<sup>®</sup>) gauze smoothly over the burn, cover this with soft pads or other absorbent dressings, and secure firmly in place with stockinet or elastic or gauze bandage. The application of antibiotics and chemotherapeutic agents to the surface of extensive burns is contraindicated because of the danger of toxic or sensitivity reactions.

**5 Exposure treatment** In this form of treatment, no dressings or medications are applied to the burn after cleansing and debridement. On exposure to air, a coagulum of serum seals the burn wound. This is the preferred method of treating burns of the head, neck, genitalia and perineum. It is also suitable for limited burns on one side of the trunk or extremity. In mass casualties it may be necessary to treat extensive burns in this manner. The patient is placed on clean sheets and turned frequently when burns encircle the body in order to avoid maceration. If infection occurs beneath it, the coagulum should be removed and warm saline compresses applied to the area.

**C Prevention of Infection** Reliance is placed on thorough cleansing of the burn and on aseptic dressing techniques. Prophylactic antibiotics are rarely used. Cultures are obtained from exudates and specific antibiotics chosen on the basis of sensitivity studies when signs of infection appear.

D Immunization against tetanus (see p 643) should be given during the first 24 hours in all major burns.

#### Burns of Specific Anatomic Areas.

A Respiratory tract burns should be suspected whenever extensive burns of the head and neck occur. Inhalation of flame or hot gases produces severe tracheobronchitis and pneumonitis. Obstructive laryngeal edema may develop rapidly, preceded by stridor, copious respiratory tract secretions, dyspnea and cyanosis. Tracheostomy should be done without delay if there is significant obstruction or retained secretions. It is justifiable to give penicillin, one million units, and streptomycin, 0.5 Gm., every 12 hours empirically in respiratory tract burns until sputum cultures can be obtained and specific antibiotics chosen.

B Head and neck burns are treated by exposure (see above). They are often less deep than first suspected, and rapid healing is favored by the great vascularity of the region. Early grafting of eyelid burns is especially important to avoid ectropion and corneal ulceration due to exposure.

C In hand burns the skin must be carefully cleaned and the fingers dressed individually with petrolatum gauze. Remove rings. Immobilize the entire hand in the position of function by means of pressure dressings and splints. Soon after the first re-dressing, which is done 5-8 days after the burn, areas of third degree burn should be excised in a bloodless field (using a pneumatic tourniquet) and a skin graft applied in order to obtain the earliest possible restoration of function.

D Joint areas should be maintained in optimal position and all third degree involvement grafted early to avoid disabling contractures.

E Burns of the perineum and genitalia are left exposed and cleaned with soap and water when they become soiled with feces or urine. An indwelling Foley catheter for constant drainage of the bladder may be advisable in genital burns.

### LATER CARE OF THE BURN WOUND

#### Re-dressing & Re-evaluation.

Observe strict aseptic technique in all burn dressings. Remove the original burn dressing

down to the petrolatum gauze after 5-8 days. The depth and extent of the burn can be accurately determined at this time. Second degree burns require only reapplication of the pressure dressing and should heal in about 2 weeks. Third degree burns demand special management.

#### Treatment of Third Degree Burns.

A Removal of Slough. The necrotic surface of a third degree burn usually does not separate for many weeks. Significant areas of slough or necrosis should therefore be carefully removed in the operating room under general anesthesia 10-14 days after the burn if the patient's general condition allows. Burns of the face permit more conservative debridement since slough separates rapidly in this region.

B Skin Grafting. Early skin grafting (preferably within the first few weeks following the burn) is essential to avoid chronic sepsis, malnutrition, and scar contractures. Skin grafting should be started as soon after removal of slough as possible. The denuded granulating surfaces should be firm and bright red, with a minimum of exudate. Warm saline dressings (which must be changed several times daily) may be of great assistance in the final preparation of the burn wound for skin grafting. Multiple changes of dressing and debridement under general anesthesia may be required. Application of preserved cadaver skin homografts will sometimes tide over the extensively burned patient until autografting can be accomplished.

C Control of Infection. Signs of infection including rising temperature, tachycardia, general toxicity, local pain and tenderness, and increased drainage. Pockets of pus trapped beneath slough must be sought and liberated by debridement. Warm saline dressings (changed several times daily) are applied to infected areas. Cultures are taken and antibiotics chosen by sensitivity studies. Prolonged antibiotic therapy is not necessary if drainage and dressings are adequate. Skin grafts will not survive a virulent, invasive infection, but grafting should be done as soon as the infection is under control. Daily immersion in a tub of warm water containing hexachlorophene (G-11) soap is a useful adjunct in extensive chronic burns.

#### General Supportive Measures.

Chronic infection, exudative loss of protein, the catabolic response to atresia, and the anorexia and depression caused by pain

and toxemia can produce rapid nutritional depletion in the severely burned patient. The anemia that is often present is caused by hemolysis at the time of burning and subsequent inhibition of erythropoiesis by infection. These changes must be prevented by administering a high-caloric, high-protein intake at the outset of therapy and giving vitamin supplements and blood transfusions to keep the hemoglobin above 12 Gm. Protein anabolic steroids have been recommended (see p 581). ACTH or the cortisones are not indicated unless there is specific evidence of adrenocortical insufficiency. It is generally felt that they increase susceptibility to infection.

Artz, C P., & B H. Gaston. A reappraisal of the exposure method in the treatment of burns: donor sites and skin grafts. *Ann Surg* 151 939-50, 1960.

Moore, F G. Burns: an annotated outline for practical treatment. *M Clin North America* 38 1201-14, 1952.

Young, J M., & G W. Hyatt. Stored skin homografts in extensively burned patients. *Arch Surg* 80 208-13, 1960.

gen may be of value. Mouth-to-mouth respiration should never be delayed or discontinued during transportation of the patient or in attempting to procure oxygen apparatus, airways, a defibrillator, or other equipment. Artificial respiration should be continued as long as the heart is still beating, no matter how faintly. If ventricular fibrillation occurs, artificial respiration should be combined with closed-chest cardiac massage (see p 208) and when available, external electrical defibrillation (see p 208). In cases of near drowning from salt water, examination of the blood may indicate the need for plasma infusions to correct hemoconcentration, electrolyte disturbances or hypovolemia. Specific treatment measures for near drowning in salt water, as contrasted with fresh water, have not been clearly defined and require further investigations.

Bowden, K. Drowning. *M J Australia* 1 39-43, 1957.

Redding, J S., & others. Resuscitation from drowning. *J A M A* 178 1138-40, 1961.

## DROWNING

Drowning is the fourth leading cause of accidental death in the U S A. The number of deaths due to drowning could undoubtedly be significantly reduced if adequate preventive and first aid instruction programs were instituted. Swimming instruction should be given to as many people as possible at an early age. Private swimming pools should be properly enclosed; public pools should have trained lifeguards and hazardous swimming areas should be properly posted. As many individuals as possible should be taught the proper technique of artificial respiration. Compulsory teaching of artificial respiration to school children has been suggested.

Spontaneous recovery usually occurs in victims of near drowning. If the victim is not breathing, institute immediate artificial respiration by fully extending the victim's head and blowing intermittently through his mouth or nose (see p 166). Artificial respiration should be given priority over attempts to 'drain water' from the victim. The prone position is not superior to the supine position with respect to drainage of water from the lungs. If intermittent positive pressure equipment is available, administration of 100% oxy-

gen may be of value. Mouth-to-mouth respiration should never be delayed or discontinued during transportation of the patient or in attempting to procure oxygen apparatus, airways, a defibrillator, or other equipment. Artificial respiration should be continued as long as the heart is still beating, no matter how faintly. If ventricular fibrillation occurs, artificial respiration should be combined with closed-chest cardiac massage (see p 208) and when available, external electrical defibrillation (see p 208). In cases of near drowning from salt water, examination of the blood may indicate the need for plasma infusions to correct hemoconcentration, electrolyte disturbances or hypovolemia. Specific treatment measures for near drowning in salt water, as contrasted with fresh water, have not been clearly defined and require further investigations.

Direct current is much less dangerous than alternating current. Alternating current of high frequency or high voltage may be less dangerous than low frequency or low voltage. With alternating currents of 25-300 cycles, low voltages (below 220) tend to produce ventricular fibrillation, high voltages (over 1000) respiratory failure. Intermediate voltages (220-1000) both. Electric burns are usually sharply demarcated, round or oval, painless gray areas with inflammatory reaction. Little happens to them for several weeks, sloughing then occurs slowly over a fairly wide area. Electric shock may produce momentary or prolonged loss of consciousness. With recovery there may be muscular pain, fatigue, headache and nervous irritability. The physical signs vary according to the action of the current. With ventricular fibrillation no heart sounds or pulse can be found and the patient is unconscious. The respirations continue for a few minutes, becoming exaggerated as asphyxia occurs and then ceasing as death intervenes. With respiratory failure, respirations are absent and the patient is unconscious, the pulse can be felt, but there is a marked fall in BP and the skin is cold and cyanotic.

## ELECTRIC SHOCK

## Treatment.

## A. Emergency Measures

1. Free the victim from the current at once. This may be done in many ways, but the rescuer must protect himself. Turn off the power, sever the wire with a dry wooden-handled axe, make a proper ground to divert the current, or drag the victim carefully away by means of dry clothing or a leather belt.

2. Artificial respiration must be started immediately (see p. 166) if breathing is depressed or absent, and continued until spontaneous breathing returns or rigor mortis sets in.

3. Perform precordial compression (see p. 208) for ventricular fibrillation or arrest. Artificial respiration will not restore normal heart action, and other measures may not either. Incision of the chest and manual pumping of the heart may be employed as a last resort. Electric defibrillators may be employed if available.

4. Treat shock promptly (see p. 3).

5. Positive pressure oxygen with CO<sub>2</sub> may be used when available, or oxygen and CO<sub>2</sub> by mask combined with artificial respiration.

## B. Hospital Measures:

1. Hospitalize the patient when revived and observe for sudden cardiac dilatation or secondary hemorrhage.

2. Perform lumbar puncture if signs of increased pressure are noted.

3. Treat burns conservatively. The direction and extent of tissue injury may not be apparent for weeks. Infection is usually not a problem early. Patience and delay are important in treatment, allow granulation tissue to be well established before attempting surgery. Hemorrhage may occur late and may be severe.

Kragh, L. V., & J. B. Erich. Treatment of severe electric injuries. *Am J. Surg* 101: 419-27, 1961.

Lynch, M. J. G., & P. H. Shorthouse. Injuries and death from lightning. *Lancet* 1:473-8, 1949.

## IRRADIATION REACTIONS

The effects of radiation may develop during or after the course of therapeutic x-ray or radium administration or after any exposure to ionizing radiation (e. g., x-rays, neutrons, gamma rays, alpha or beta particles). The harmful effects of radiation are deter-

mined by the degree of exposure, which in turn depends not only upon the quantity of radiation delivered to the body but also the type of radiation, which tissues of the body are exposed, and the duration of exposure. Three hundred to 500 r (400-600 rads) of x-ray or gamma radiation applied to the entire body at one time would probably be fatal. (For purposes of comparison, a routine chest x-ray delivers about 0.3 r.) Tolerance to radiation is difficult to define and there is no firm basis for evaluating radiation effects for all types and levels of irradiation. The maximum permissible daily occupational total body exposure for radiation workers has been established at 5 rem/year (multiplied by number of years of age > 18) by the Federal Radiation Council (May, 1960).

Approximate Relationship  
Between Biologic Effects & Annual  
Exposure to Radiation

General public	500 mre n*
Workers in Atomic Energy Commission facilities	5000 mrem
First identifiable signs of radiation effect	50,000 mrem
Radiation sickness appears	100,000 mrem
First deaths from radiation sickness	200,000 mrem
50% of exposed will die of radiation sickness	500,000 mrem

\*rem = roentgen equivalents man (or mammal), a unit of biologic radiation effect. mrem = 1/1000 rem

ACUTE (IMMEDIATE) RADIATION  
EFFECTS ON NORMAL TISSUES

## Clinical Findings.

A. Injury to Skin and Mucous Membranes: Irradiation causes erythema, epilation, destruction of fingernails, or epidermolysis, depending upon the dose.

## B. Injury to Deep Structures

1. Hematopoietic tissues - Injury to the bone marrow may cause diminished production of blood elements. Lymphocytes are most sensitive, polymorphonuclear leukocytes next most sensitive, and erythrocytes least sensitive. Damage to the blood-forming organs may vary from transient depression of one or more blood elements to complete destruction.

2. Blood vessels - Smaller vessels (the capillaries and arterioles) are more readily damaged than larger blood vessels. If injury is mild, recovery occurs.

3. Gonads - In males, small single doses of radiation (200-300 r) cause spermatogenesis and larger doses (600-800 r) may cause sterility. In females, single doses of 200 r may cause temporary cessation of menses and 500-800 r may cause permanent castration. Moderate to heavy radiation of the embryo in utero results in injury to the fetus or to embryonic death and abortion.

4. Lungs - High or repeated moderate doses of radiation may cause pneumonitis.

5. The salivary glands may be depressed by radiation, but relatively large doses may be required.

6. Stomach - Gastric secretion may be temporarily (occasionally permanently) inhibited by moderately high doses of radiation.

7. Intestines - Inflammation and ulceration may follow moderately large doses of radiation.

8. The normal thyroid, pituitary, liver, pancreas, adrenals, and bladder are relatively resistant to radiation.

9. The brain and spinal cord may be damaged by high doses of radiation because of impaired blood supply.

10. Peripheral and autonomic nerves are highly resistant to radiation.

### C. Systemic Reaction (Radiation Sickness)

The basic mechanisms of radiation sickness are not known. Anorexia, nausea, vomiting, weakness, exhaustion, lassitude, and in some cases prostration may occur, singly or in combination. Radiation sickness associated with x-ray therapy is most likely to occur when the therapy is given in large dosage to large areas over the abdomen, less often when given over the thorax, and rarely when therapy is given over the extremities. With protracted therapy, this complication is rarely significant. The patient's psychologic reaction to his illness or to the treatment plays an important role in aggravating or minimizing such effect.

### Prevention.

Persons handling radiation sources can minimize exposure to radiation by recognizing the importance of time, distance, and of shielding. Areas housing x-ray and nuclear materials must be properly shielded. Untrained or poorly trained personnel should not be permitted to work with x-ray and nuclear radiation. Any unnecessary exposures, diagnostic or therapeutic, should be avoided. X-ray equipment should be periodically checked for reliability of output, and proper filters

should be employed. When feasible, it is advisable to shield the gonads, especially of young persons. Fluoroscopic examination should be performed as rapidly as possible, using an optimal combination of beam characteristics and filtration, the tube-table distance should be at least 18 inches and the beam size should be kept to a minimum required by the examination. Special protective clothing may be necessary to protect against contamination with radioisotopes. In the event of accidental contamination, removal of all clothing and vigorous bathing with soap and water should be followed by careful instrument (Geiger counter) check for localization of ionizing radiation.

### Treatment.

There is no specific treatment for the biologic effects of ionizing radiation. The success of treatment of local radiation effects will depend upon the extent, degree, and location of tissue injury. Treatment is supportive and symptomatic.

A systemic radiation reaction following radiation therapy (radiation sickness) is preferably prevented, but when it does occur it is treated symptomatically and supportively. The antinauseant drugs, e.g., dimenhydrinate (Dramamine<sup>®</sup>), 100 mg. one hour before and one hour and 4 hours after radiation therapy may be of value. Whole blood transfusions may be necessary if anemia is present. Transfusion of marrow cells has been employed recently. Disturbances of fluid or electrolyte balance require appropriate treatment. Antibiotics may be of use in the event of secondary infection.

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Gerstner, H.B. • Acute clinical effects of penetrating nuclear radiation. J.A.M.A. 158:381-8, 1958.

Hempelmann, L.H., Lisco, H., & J.G. Hoffman. The acute radiation syndrome: a study of nine cases and a review of the problem. Ann Int Med 36:279-510, 1952.

Warren, S. Radiation protection. New England J Med 264:705-11, 1961.

### DELAYED (CHRONIC) EFFECTS OF EXCESSIVE DOSES OF IONIZING RADIATION

### Clinical Findings.

#### A. Somatic Effects:

1. Skin acarring, atrophy, and telangiectases, obliterative endarteritis, pulmonary



fibrosis, intestinal stenosis, and other late effects may occur.

2. Cataracts may occur following irradiation of the lens.

3. Leukemia may occur, perhaps only in susceptible individuals, many years following radiation. Under the usual conditions of radiation therapy this is rare; the incidence of cataracts in properly protected radiation workers should be the same as in the general population.

4. The incidence of neoplastic disease is increased in persons exposed to large amounts of radiation, particularly in areas of heavy damage.

5. Microcephaly and other congenital abnormalities may occur in children exposed in utero, especially if the fetus was exposed during the first 4 months of pregnancy.

B. Genetic Effects: Alteration of the sex ratio at birth (fewer males than females) suggests genetic damage. The incidence of congenital abnormalities, stillbirths, and neonatal deaths when conception occurs after termination of radiation exposure is apparently not increased.

#### Treatment.

See treatment of acute radiation reactions

Hollingsworth, J.W.: Delayed radiation effects in survivors of the atomic bombings: a summary of the findings of the Atomic Bomb Casualty Commission, 1947-1959. New England J. Med. 263:481-7, 1960.

Leading article: Genetic hazard of medical x-rays. Lancet 2:1285-6, 1960

Multiple authors: The medical consequences of thermonuclear war. New England J Med 266:1126-49, 1962.

### DECOMPRESSION SICKNESS (Caisson Disease, Bends)

Decompression sickness has long been known as an occupational hazard of professional divers who are involved in deep-water exploration, rescue, salvage, or construction, and professional divers and their surface supporting teams are familiar with the prevention, recognition, and treatment of this disease. In recent years the sport of scuba (self-contained underwater breathing apparatus) diving has become very popular, and a large number of un-

trained individuals are exposed to, but unfamiliar with, the hazards of decompression sickness.

At low depths the greatly increased pressure (e.g., at 100 feet the pressure is 4 times greater than at the surface) compresses the respiratory gases into the blood and other tissues. During ascent from depths greater than 30 feet, gases dissolved in the blood and other tissues escape as the external pressure decreases. The appearance of symptoms is dependent upon the depth and duration of submersion, the degree of physical exertion, the age, weight, and physical condition of the diver, and the rate of ascent. The size and number of the gas bubbles (notably nitrogen) escaping from the tissues is dependent upon the difference between the atmospheric pressure and the partial pressure of the gas dissolved in the tissues. It is the release of gas bubbles, and particularly the location of their release, which determines the symptoms.

Decompression sickness may also occur in rapid ascents from sea level to high altitudes when there is no adequate pressurizing protection.

The onset of symptoms occurs within 30 minutes in half of cases and almost invariably within 6 hours. Symptoms, which are highly variable, include pain (largely in the joints), pruritic rash, visual disturbances, weakness or paralysis, dizziness or vertigo, headache, dyspnea, paresthesias, aphasia, and coma.

Early recognition and prompt treatment are extremely important. Continuous administration of oxygen is indicated as a first aid measure, whether or not cyanosis is present. Acetylsalicylic acid may be given for pain, but narcotics should be used very cautiously since they may obscure the patient's response to recompression. Rapid transportation to a treatment facility for recompression is necessary not only to relieve symptoms but to prevent permanent impairment. The physician should be familiar with the nearest recompression center. The local public health department or nearest naval facility should be able to provide such information.

Dewey, A.W., Jr.: Decompression sickness, an emerging recreational hazard. New England J. Med. 267:759-66 and 812-20, 1962.

## MEDICAL EFFECTS OF AIR TRAVEL & SELECTION OF PATIENTS FOR AIR TRAVEL

The decision about whether or not it is advisable for a patient to travel by air depends not only upon the nature and severity of the illness but also upon such factors as the duration of flight, the altitude to be flown, pressurization, the availability of supplementary oxygen, the presence of trained nursing attendants, and other special considerations. Medical hazards or complications of modern air travel are remarkably uncommon. The Air Transport Association of America defines an incapacitated passenger as "one who is suffering from a physical or mental disability and who, because of such disability or the effect of the flight on the disability, is incapable of self-care, would endanger the health or safety of such person or other passengers or airline employees, or would cause discomfort or annoyance of other passengers."

### Cardiovascular Disease

**A. Cardiac Decompensation:** Patients in congestive failure should not be permitted to fly until they are compensated by appropriate treatment, or unless they are in a pressurized plane with 100% oxygen therapy available during the entire flight.

**B. Compensated Valvular or Other Heart Disease:** Patients should not fly over 8000-9000 feet unless aircraft is pressurized and oxygen is administered at altitudes approaching or above 8000 feet.

**C. Acute Myocardial Infarction, Convalescent and Asymptomatic:** At least 6-8 weeks of convalescence are recommended even for asymptomatic patients if flying is contemplated. Oxygen should be available.

**D. Angina Pectoris:** If slight physical exertion produces anginal pain, air travel is inadvisable. In mild to moderate cases of angina, air travel may be permitted, especially in pressurized planes. Oxygen should be available.

**E. Hypertension:** Ordinarily, there are no contraindications to air travel for hypertensive patients unless there are symptoms or signs of impending cerebrovascular accident. Mild sedatives are recommended for most patients.

### Respiratory Disease.

**A. Asthma:** Patients with mild asthma can travel without difficulty. Patients with status asthmaticus should not be permitted to fly.

**B. Pneumonia:** Unless there is marked impairment of pulmonary function, pneumonia patients may fly if oxygen is available.

**C. Tuberculosis:** Patients with active, communicable tuberculosis or pneumothorax should not be permitted to travel by air.

**D. Bronchiectasis, pulmonary abscess, or lung cancer** patients may be flown safely unless there is marked impairment of pulmonary function.

### Anemia.

If hemoglobin is less than 8-9 Gm./100 ml., oxygen should be available. Patients with severe anemia should not travel until hemoglobin has been raised to a reasonable level.

### Diabetes Mellitus

Diabetics who do not need insulin or who can administer their own insulin during flight may fly safely. "Brittle" diabetics who are subject to frequent episodes of hypoglycemia should be in optimal control before flying and should carry sugar or candy in case hypoglycemic reactions occur.

### Contagious Diseases.

Patients with contagious diseases are not permitted to travel by passenger (scheduled) airlines at any time.

### Postoperative Patients.

Patients convalescing from thoracic or abdominal surgery should not fly until 10 days after surgery, and then only if their wound is healed and there is no drainage.

### Colostomy

Patients may be permitted to travel by air providing they are nonodorous and colostomy bags are emptied before flight.

### Hernias.

Patients with large hernias, unsupported by a truss or binder, should not be permitted to fly because of an increased danger of strangulation.

### Postsurgical or Post-traumatic Eye Cases.

Pressurized cabins and oxygen therapy are necessary to avoid retinal damage due to hypoxia.

**Psychoses**

Severely psychotic agitated or disturbed patients should not be permitted to fly even when accompanied by a medical attendant

**Neuroses**

Extremely nervous or apprehensive patients may travel by air if they receive adequate sedatives or tranquilizers before and during flight

**Motion Sickness**

Patients subject to motion sickness should receive either sedatives or antihistamines [e.g. dimenhydrinate (Dramamine<sup>®</sup>) or meclizine (Bonine<sup>®</sup>)] 50 mg q.i.d. before and during the flight. Small meals of easily digested food before and during flight may reduce the tendency to nausea and vomiting.

**Pregnancy**

Pregnant women may be permitted to fly during the first 8 months of pregnancy unless there is a history of habitual abortion or premature birth. During the ninth month of pregnancy a statement must be furnished that delivery is not due within 72 hours of destination time.

**Early Infancy**

Infants less than one week old should not be flown at high altitudes or for long distances.

Dowd K E. Medical Aspects of Air Travel. Modern Medicine. May 1 1960.

Hultgren H N & E Lundberg. Medical problems of high altitudes. Mod Concepts Cardiovas Dis 31 719 24 1962.

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Bedwell T C Jr & others. Medical and public health aspects of nuclear weapons incidents in peacetime. U S Armed Forces M J 11 961 90 1960.

Behrens C F (editor). Atomic Medicine. 3rd ed. Williams & Wilkins 1959.

Borden D L, Waddill J F & G S Brier III. Statistical study of 265 cases of heat disease. J A M A 128 1200 5 1945.

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Kleitsch W P & E K Connors. Cold injuries of the extremities. Postgrad Med 16 191 200 1954.

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Parkes A S (editor). Hypothermia and the effects of cold. Brit M Bull 17 1 73 1961.

Recommendations of the symposium on emergency resuscitation. WHO Committee report. J A M A 178 748 1961.

Schlegel J V & H Jorgensen. Studies in metabolism of trauma II Treatment of burns. Ann Surg 148 251 66 1959.

Shafer J C & A W Thompson. Local cold injury: a report of sequelae. Arch Dermat 72 335 47 1955.

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## Poisons

Robert H Dreisbach

### DIAGNOSIS OF POISONING

The diagnosis of poisoning, when not obvious, depends in great measure upon considering the possibility that poisoning has occurred. Once the physician includes poisoning in his differential diagnosis, he will be more likely to take the necessary steps to confirm or reject this possibility.

In general, the steps leading to a diagnosis of poisoning are as follows:

(1) Question the patient or his relatives or co-workers carefully concerning the presence of poisons in the environment.

(2) Take a careful history and perform a complete physical examination.

(3) Take samples for laboratory evaluation of damage to specific organs and to confirm or rule out exposure to specific poisons.

Cases of poisoning generally fall into 3 categories: (1) exposure to a known poison, (2) exposure to an unknown substance which may be a poison, and (3) disease of undetermined etiology in which poisoning must be considered as part of the differential diagnosis.

### EXPOSURE TO KNOWN POISONS

In most cases of poisoning, the agent responsible is known and the physician's only problem is to determine whether the degree of exposure is sufficient to require more than emergency or first aid treatment. The exact quantity of poison absorbed by the patient will probably not be known, but the physician may be able to estimate the greatest amount which the patient could have absorbed by examining the container from which the poison was obtained and comparing the missing quantity with the known fatal dose. Reported minimum lethal doses are useful indications of the relative hazards of poisonous substances, but the fatal dose may vary greatly. If the poison is

known to have caused serious or fatal poisoning, treatment for exposure to any quantity must be vigorous.

### EXPOSURE TO SUBSTANCES WHICH MAY BE POISONOUS

If a patient has been exposed to a substance whose ingredients are not known, the physician must identify the contents without delay. The following sources are suggested for identifying the contents of trade-named mixtures.

#### Call Poison Information Center.

Obtain the telephone number of the nearest Poison Information Center from the local medical society or from the Physician's Desk Reference. Make certain that 24-hour service is available. Poison information centers are in most cases able to identify the ingredients of trade-named mixtures, give some estimate of their toxicity, and suggest the necessary treatment.

#### Books.

Since available proprietary mixtures number in the hundreds of thousands, it is impractical to include all of these names in a single reference work. However, a number of books are useful in determining the contents of mixtures and should be available to every physician.

1. Pesticide Handbook (annual publication), by D. E. F. Frear. College Science Publishers, Box 798, State College, Pa. (Lists 9000 pesticide mixtures.)

2. Clinical Toxicology of Commercial Products, by M. N. Gleason, R. E. Gosselin, and H. C. Hodge. Williams & Wilkins, 1957. (Lists ingredients of approximately 12,000 household products.)

3. The Merck Index, Seventh Edition. Merck and Co., Inc., 1960.

4. Modern Drug Encyclopedia, Eighth Edition. Edited by Harry D. Fein. Reuben

H. Donnelly Corporation, 1961. (Lists 4000 proprietary medicinal agents.)

5. New and Nonofficial Drugs (annual publication) J.B. Lippincott Co

6 Physician's Desk Reference (annual publication). Medical Economics, Inc. (Lists 6500 proprietary medicinal agents.)

7. Handbook of Poisoning Diagnosis and Treatment, by R.H. Dreisbach Lange Medical Publications, 1961. (Lists 6000 poisons and trade-named mixtures)

8. Clinical memoranda on economic poisons. U.S. Public Health Service Publ. No. 476. Government Printing Office, 1956.

9. A selective list of drugs used in psychiatry. Psychopharmacology Service Center Bull. Vol. 1, No. 2, March 1962. (Toxicity and side effects of tranquilizers.)

### The Manufacturer or His Local Representative.

Another way to identify the contents of a substance which may be poisonous is to telephone the manufacturer or his representative. He may also have information concerning the type of toxic hazard to be expected from the material in question, and may know methods of treatment.

## DIFFERENTIAL DIAGNOSIS OF DISEASES WHICH MAY BE THE RESULT OF POISONING

In any disease state of questionable etiology, poisoning must be considered as part of the differential diagnosis. For example, the high incidence of cases of lead poisoning which have been discovered in a few medical centers in recent years indicates that many cases must go unrecognized. Some of these patients had symptoms for more than a year and had been seen by several physicians before the diagnosis was made. Admittedly, the diagnosis of lead poisoning is difficult, but the possibility of this disorder must be considered before the necessary steps to confirm the diagnosis can be taken. Most important of the confirmatory steps in any case of poisoning is the discovery of a source of the poison and a history of exposure to it.

In making the differential diagnosis of a disease which may be the result of poisoning, the number of poisons which must be considered in any particular case can be reduced by classifying exposure possibilities. A convenient classification based on exposure consists of the following groups: (1) household, (2) medicinal, (3) industrial, (4) agricultural, and (5) natural.

## HISTORY & PHYSICAL EXAMINATION

### Symptom History.

#### A. General Health.

1. Weight loss - Any chronic poisoning, but especially lead, arsenic, dinitrophenol, thyroid, mercury, and chlorinated hydrocarbons

2. Asthenia - Lead, arsenic, mercury, chlorinated organic compounds

3. Loss of appetite - Trinitrotoluene.

#### B. Head and CNS

1. Delirium, hallucinations - Alcohol, antihistamines, atropine and related drugs, camphorated oil, lead, cannabis (marijuana), cocaine, amphetamine, bromides, quinacrine, ergot, santonin, rauwolfia, salicylates, phenylbutazone, methyl bromide, chlorophenothane (DDT), chlordane

2. Depression, drowsiness, coma - Barbiturates or other hypnotics, alcohol, solvents, antihistamines, insecticides or rodenticides, atropine or related drugs, cationic detergents, lead, opium and opium derivatives, paraldehyde, cyanides, carbon monoxide, alcohols, phenol, chenopodium, santonin, aspidium, salicylates, chlorpromazine, akee

3. Muscular twitchings and convulsions - Insecticides, strychnine and brucine, camphor, atropine, aspidium, cyanides, santonin, ethylene glycol, nicotine, black widow spider

4. Headache - Glyceryl trinitrate (nitroglycerin), nitrates, nitrites, hydralazine, trinitrotoluene

#### C. Eyes

1. Blurred vision - Atropine, physostigmine, phosphate ester insecticides, cocaine, solvents, dinitrophenol, nicotine, aspidium, methyl alcohol.

2. Colored vision - Santonin, aspidium, digitalis

3. Double vision - Alcohol, barbiturates, nicotine, phosphate ester insecticides.

#### D. Ears

1. Tinnitus - Quinine, salicylates, quinidine.

2. Deafness or disturbances of equilibrium - Streptomycin, dihydrostreptomycin, quinine.

#### E. Nose

1. Anosmia - Phenol nose-drops, chromium.

2. Fotor nasalis - Chromium

#### F. Mouth

1. Loosening of teeth - Mercury, lead, phosphorus.

2 Painful teeth - Phosphorus, mercury, bismuth

3 Dry mouth - Atropine and related drugs.

4 Salivation - Lead, mercury, bismuth, thallium, phosphate ester insecticides other heavy metals

#### G Cardiorespiratory System

1 Respiratory difficulty, including dyspnea on exertion and chest pain - Phosphate ester insecticides, salicylates, botulism, nickel carbonyl, black widow spider, scorpion, shellfish, fish, physostigmine, silicosis, other pneumoconioses, cyanide, carbon monoxide, atropine, strychnine

2 Palpitation - Nitrites, glyceryl trinitrate (nitroglycerin), organic nitrates

3 Cough - Smoke, dust, silica, beryllium

#### H Gastrointestinal System

1 Vomiting, diarrhea, abdominal pain - Caused by almost all poisons, particularly corrosive acids or alkalis, metals, phenols, medicinal irritants, solvents, cold wave neutralizer, food poisoning

2 Jaundice - Chlorinated compounds, arsenic and other heavy metals, chromates, cinchophen, neocinchophen, mushrooms, phenothiazines, sulfonamides, chlorpromazine, ethylene chlorhydrin, trinitrotoluene, aniline

3 Blood in stools - Warfarin

#### I Genitourinary

1 Anuria - Mercurials, bismuth, sulfonamides, carbon tetrachloride, formaldehyde, phosphorus, ethylene chlorhydrin, turpentine, oxalic acid, chlordane, castor bean, jequirity bean, trinitrotoluene

2 Polyuria - Lead

3 Menstrual irregularities - Estrogens, lead, bismuth, mercurials, other heavy metals

4 Color of urine - Warfarin (red), fava beans (red), hepatotoxins (orange)

#### J. Neuromuscular System

1 Muscular weakness or paralysis - Lead, arsenic, botulism, poison hemlock (Conium maculatum), organic mercurials, thallium, tri-orthocresyl phosphate, chlorophenothane (DDT), chlordane, shellfish

2 Muscle fasciculations - Phosphate ester insecticides, nicotine, black widow spider, scorpion

#### K. Endocrine System

1. Libido decreased - Lead, mercury, other heavy metals

2. Breast enlargement - Estrogens

#### L. Anemia Lead, benzene

### Physical Examination

#### A. General

1 BP fall - Nitrates, nitrites, glyceryl trinitrate (nitroglycerin), veratrum, cold wave neutralizer, acetanilid, chlorpromazine, quinine, chenopodium, volatile oils, aconite, disulfiram, iron salts, methyl bromide, arsine, phosphine, nickel carbonyl, stibine

2 BP rise - Epinephrine or substitutes, veratrum, ergot, cortisone, vanadium, lead, nicotine

3 Tachycardia - Potassium bromate

4 Bradycardia - Veratrum, zygadenus

5 Fever - Dinitrophenol or other nitrophenols, jimson weed (atropine), boric acid

6 Hypothermia - Akee

#### B Skin

1 Cyanosis in the absence of respiratory depression or shock - Methemoglobinemia from aniline, nitrobenzene, acetanilid, phenacetin, nitrate from well water or food, bismuth subnitrate, cloth marking ink (aniline), chloramine-T.

2 Dryness - Atropine and related compounds

3 Corrosion or destruction - Acids or alkalies, permanganate

4 Jaundice from liver injury - Chlorinated compounds, arsenic, chromates, cinchophen, neocinchophen, mushrooms, phenothiazine and sulfonamides

5 Jaundice from hemolysis - Aniline, nitrobenzene, pamaquine, pentaquine, primaquine, benzene, castor beans, jequirity beans, fava beans, phosphine, arsine, nickel carbonyl

6 Redness - Carbon monoxide, cyanide

7 Rash - Bromides, sulfonamides, antibiotics, poison oak, hair preparations, photographic developers, salicylates, trinitrotoluene, chromium, phenothiazine, gold salts, chlorinated compounds

8 Loss of hair - Thallium

#### C Eyes

1 Dilated pupils - Atropine and related drugs, cocaine, nicotine, solvents, depressants

2 Contracted pupils - Morphine and related drugs, physostigmine and related drugs, phosphate ester insecticides

3 Pigmented scleras - Quinacrine, san-tonin, jaundice from hemolysis or liver damage

4 Pallor of optic disk - Quinine, nicotine, carbon disulfide

#### D Perforated Septum Chromium

**E. Mouth**

- 1 Black line on gums - Lead, mercury, arsenic, bismuth
- 2 Inflammation of gums - Lead, mercury, arsenic, bismuth, other heavy metals
- 3 Salivation - Phosphate ester insecticides, mercury, mushrooms

**F. Lungs**

- 1 Wheezing - Phosphate ester insecticides, physostigmine, neostigmine, mushrooms (*Amanita muscaria*)
- 2 Decreased vital capacity - Silica, beryllium dusts, other dusts
- 3 Rapid respirations - Cyanide, atropine, cocaine, carbon monoxide, carbon dioxide
- 4 Slow respirations - Cyanide, carbon monoxide, barbiturates, morphine, botulism, aconite, magnesium
- 5 Pulmonary edema - Metal fumes, hydrogen sulfide, methyl bromide, methyl chloride

**G. Central Nervous System**

- 1 Convulsions - Insecticides, strychnine camphor, atropine
- 2 Depression, drowsiness, coma - Barbiturates or other hypnotics, alcohol, solvents, antihistamines, insecticides or rodenticides, atropins or related drugs, lead, opium and derivatives, paraldehyde, cyanides, carbon monoxide, alcohols, phenol
- 3 Deafness or disturbances of equilibrium - Streptomycin, dihydrostreptomycin, neomycin, quinine
- 4 Mental deterioration - Thallium, lead, mercury

**H. Muscles**

- 1 Muscle weakness or paralysis (may be limited to a single muscle or muscle group) - Lead, arsenic, botulism, poison hemlock (*Conium maculatum*), organic mercurials, tri-ortho-cresyl phosphate, carbon disulfide, insecticides
- 2 Muscle twitching - Insecticides, nicotine, manganese, shellfish, chlorophenothane (DDT),

**B. Blood Bromide** The La Motte Chemical Company, Towson, Baltimore 4, Maryland, has available a simplified procedure for determining blood bromide levels. The test is carried out by adding gold chloride reagent to 2 ml of deproteinized blood serum. The resulting color reaction is compared with a known bromide standard until a color match is obtained. The blood bromide concentration is then derived by reading directly from the standard color tube. An instruction book gives each step in detail. Blood bromide levels above 150 mg / 100 ml of serum produce symptoms of intoxication, levels above 200 mg / 100 ml are associated with serious toxicity.

**C. Urine Bromide and Iodine** To 10 ml of urine add a few drops of fuming nitric acid and 5 ml of chloroform, mix gently and let stand 3 minutes. The chloroform settles to the bottom and takes on a pink to violet color in the presence of iodides or a yellow color in the presence of bromides. A positive test is not an indication of poisoning but only of absorption of bromide. The blood bromide test indicates the seriousness of poisoning.

**D. Urine Barbiturates (Modified Koppanyi Method)** Acidify 100 ml of urine with a few drops of dilute sulfuric acid and then extract by shaking with 200 ml of diethyl ether in a separatory funnel. Allow to settle, drain water layer, and filter the top ether layer through filter paper. Remove the ether by evaporation at low temperature on a water bath. If the residue is colored, dissolve it in 10 ml of 0.5 N sodium hydroxide. Acidify slightly with dilute sulfuric acid and re-extract with ether. Evaporate the ether to dryness, and dissolve the residue in 1 ml of dry chloroform. Transfer a few drops to a 6 mm test tube, add 2 drops of 1% anhydrous cobalt acetate in absolute methyl alcohol, and mix. Layer on top 5 drops of 5% isopropyl amine in absolute alcohol. A violet interface or ring indicates the presence of barbiturates. A trace of water prevents color development.

**Alternates:** The first ether extract may be washed with pH 9.0 buffer to remove interfering material before proceeding further. The acid urine may be treated with 5 Gm. of Super-Cel® to remove interfering substances. Remove the Super-Cel® by filtration before extracting with ether.

**Special Examinations**

Special chemical examinations for lead or other heavy metals, insecticides, cholinesterase, barbiturates, alkaloids, etc., may be necessary in the differential diagnosis of

**LABORATORY EXAMINATION****Simplified Laboratory Tests.**

**A. Urinary Phenolic Compounds (Salicylates, Diacetic Acid)** To 5 ml of acidified urine add 10% tincture ferric chloride drop-by-drop until precipitation ceases. A purple color indicates a positive test. (Boiling the urine eliminates diacetic acid, if present.)

## First Aid Measures in Poisoning

The following summary is provided for the physician's use in giving instructions for first aid treatment in response to an emergency inquiry. With the exceptions noted under Ingested Poison, any of these procedures can be carried out by laymen.

### Ingested Poison

Lay persons should not attempt treatment if the patient is convulsing or unconscious. If the patient has ingested corrosives (acid or alkali) or petroleum products (kerosene, gasoline, paint thinner, lighter fluid, etc.) the procedures described in paragraph 3 below should not be used.

- 1 Have the patient drink one of the following to dilute the poison and slow absorption: milk, beaten eggs, a suspension of flour, starch or mashed potatoes in water, or water.
- 2 Give universal antidote if available.
- 3 Stimulate vomiting by rubbing the pharynx and the back of the tongue with a finger or spoon handle. If vomiting cannot be started in this way, give  $\frac{1}{4}$  tsp of mustard in a glass of water.
- 4 Give a cathartic - One heaping Tbsp of sodium sulfate (Glauber's salt) dissolved in one-half glass of water by mouth.
- 5 Conserve body warmth by applying blankets. Avoid external heat.

### Inhaled Poisons

- 1 Carry the victim to fresh air immediately, loosen tight clothing.
- 2 Give artificial respiration by direct inflation (see p. 166) if respiration is depressed. Remove any objects from the patient's mouth, hold his chin up, tilt his head back as far as possible, and blow into his mouth or nose until his chest rises. Repeat 20 times/minute. Obtain a resuscitator from the police department, fire department, or medical supply service company to facilitate oxygen administration.

### Skin Contamination

- 1 Drench skin with water in tub or shower.
- 2 Direct a stream of water onto the skin while removing the patient's clothing.
- 3 Do not use chemical antidotes.

### Eye Contamination

- 1 Holding the lids apart, wash the eye for 5 minutes with running water at eye fountain or with gentle stream of water from a hose or tap.
- 2 Do not use chemical antidotes.

### Snake, Insect, or Arachnid Bite

- 1 Immobilize patient immediately.
- 2 Give specific antiserum as soon as possible.
- 3 If the patient must be moved, carry him on a stretcher as gently as possible.

### Injected Poisons (Overdoses of Drugs)

- 1 Make the patient lie down.
- 2 Apply a rubber band tourniquet (1 X 24 inches) proximal to the injection. The pulse should not disappear in vessels beyond the tourniquet nor should a throbbing sensation be felt by the patient. Loosen tourniquet for one minute in every 15.
- 3 Apply an ice pack to the site of the injection.

### Identification of Unknown Toxic Agent

The following information is useful in attempting to identify a toxic agent. It should be available when you call your Poison Information Center.

- 1 Physical state (solid, liquid, gas)
- 2 Odor
- 3 Trade-name
- 4 Use
- 5 Presence of poison label
- 6 Inflammability warning



**poisoning** The following laboratories are suggested for the performance of such analyses. It is wise to make prior arrangements with the laboratory to make certain that they will accept samples for analyses

(1) County coroner's laboratory - Heavy metals, blood alcohol, barbiturates, alkaloids

(2) City, county, or state police laboratory - Blood alcohol, barbiturates, other poisons

(3) State toxicologist's office - As under

(1) Analyses in connection with criminal poisonings

(4) Federal Bureau of Investigation Laboratory, Washington, D C (only through local police)

(5) State departments of public health (see p 75) will usually perform analyses relating only to cases of occupational poisoning insecticides, heavy metals

(6) County hospital laboratory - Lead, barbiturates, alkaloids, blood alcohol

(7) Private laboratories - Heavy metals, barbiturates

(8) Technical Development Laboratory United States Public Health Service, P O Box 769, Savannah, Georgia - insecticides in body fat, blood cholinesterase (They will send sample bottles on request by physicians)

## PRINCIPLES OF TREATMENT OF ACUTE POISONING

(See also First Aid Measures, p. 774.)

In the emergency treatment of any poisoning in which the toxin has been taken by mouth, the following general procedures should be carried out (1) Remove poison by emesis, lavage, catharsis, or diuresis as soon as possible (2) Inactivate poison with specific or general antidote Follow with lavage (3) Combat shock, collapse, and specific manifestations as they arise (4) Protect mucous membranes with demulcents

### Removal of Poison

**Caution** Do not use stomach tubes or emetics in poisonings due to strong acids or alkalies or other corrosive agents, they may cause gastric perforation

**A. Emesis** This is the quickest way to evacuate gastric contents

1 Indications - For removal of excess poison in cooperative patients, or for convenience when a stomach tube is unavailable or the patient is unable to take stomach tube

2 Contraindications - (1) Drowsy or unconscious patients (danger of aspiration of stomach contents) (2) Ingestion of corrosive poisons, kerosene, or convulsants

3 Technic - Introduce a finger into the throat, or give an emetic and follow with copious quantities of warm water Apomorphine hydrochloride, 6 mg ( $\frac{1}{10}$  gr.) subcut. will often quiet the patient and will usually induce vomiting Powdered mustard, 1-3 tsp in a glass of lukewarm water, is an uncertain and unpleasant emetic, but it has the advantage of being generally available Sodium chloride, 1 Tbsp in a glass of lukewarm water, is not very efficient but is readily available Strong soapsuds, 250-500 ml, may be used if nothing else is available

Emesis should be continued until gastric contents are clear

### B Gastric Aspiration and Lavage

1 Indications - (1) Removal of excess of noncorrosive poisons which may later be absorbed from the gastrointestinal tract (2) Removal of CNS depressant poisons when vomiting does not occur (vomiting center paralyzed) (3) For collection and examination of gastric contents for identification of poison (4) For convenient administration of antidotes

2 Contraindications - (1) Extensive corrosion of tissues by poison (2) Struggling, delirious, stuporous, or comatose patients, because of danger of aspiration pneumonia

3 Technic - Gently insert a lubricated, soft but noncollapsible stomach tube through the mouth or nose into the stomach Lavage copiously, but do not distend the stomach Under some conditions it is better to lavage with a small quantity of fluid at frequent intervals Always remove excess of lavage solution

Collect and save washings in clean containers for toxicologic examination when indicated In forensic cases, seal with sealing wax and place in a locked refrigerator, deliver to toxicologist personally and get a signed receipt If refrigeration is lacking, preserve the specimen with equal quantities of 95% alcohol, do not use formalin, as this interferes with toxicologic examination

4 Gastric lavage fluids - (1) Warm tap water or 1% salt solution (2) Thin soluble starch paste (3) Sodium bicarbonate, 1%. (4) Potassium permanganate, 1:2000 (1 Gm in 2000 ml water) (5) Sodium thiosulfate, 1% (6) Hydrogen peroxide, 1 or 2%

**C Catharsis** Sodium sulfate, 30 Gm (1 oz) in 200 ml of water, may be effective in retarding absorption

**Inactivation by Demulcents.**

Demulcents precipitate metals and also help to limit the absorption of many poisons. These bland agents are also soothing to inflamed mucous membranes. Use the whites of 3 or 4 eggs beaten in 500 ml of milk or water, skimmed milk, or thin flour or starch solution (boiled, if possible). Follow with gastric lavage.

**Supportive & Symptomatic Measures.**

The victim of acute poisoning must be kept under close observation in order to anticipate the immediate and delayed complications of the poisoning. Suicidal patients may need special surveillance and should be placed under the care of a psychiatrist.

**A Circulatory Failure**

1. Shock (see p 2) - The principal measures include recumbent position, warmth, and blood and parenteral fluids. Vasopressor agents (see p 4) are at times necessary to maintain effective BP.

2. Cardiac failure (see p 216) - The principal measures include rest, oxygen, and digitalis.

3. Pulmonary edema - Give 100% oxygen by mask. If pulmonary edema is due to gaseous irritants, give aminophylline, 0.5 Gm ( $7\frac{1}{2}$  gr) 1 V to relieve associated bronchial constriction. Pulmonary edema due to heart failure is an emergency requiring morphine, oxygen, and digitalis. Pulmonary foaming may be relieved by using 20% ethyl alcohol in the oxygen humidifier. The oxygen should be given at slightly increased pressure by means of a mask with an adjustable exit valve.

**B Respiratory Abnormalities**

1. Respiratory obstruction - Correct by oropharyngeal airway, intratracheal intubation, or tracheostomy.

2. Respiratory depression - Remove from toxic atmosphere. Administer artificial respiration *p r n*. A resuscitator or other means of automatic ventilation may be employed but requires constant supervision. Stimulants (analeptic drugs) are of questionable value even for poisoning with CNS depressant drugs. The following are used to maintain BP. Do not exceed the maximum dosages listed in 24 hours: (1) Ephedrine sulfate, 50-120 mg ( $\frac{3}{4}$ -2 gr) orally or subcut. (2) Amphetamine sulfate, 5-40 mg ( $\frac{1}{12}$ -2/3 gr) orally or 1 V.

3. Hypostatic pneumonia - The principal measures include antibiotics and intratracheal aspiration *p r n*.

**C CNS Involvement**

1. CNS excitement - Use hypnotic or anticonvulsant drugs. (1) Amobarbital sodium

(Amytal®), 250-500 mg ( $3\frac{3}{4}$ -7 $\frac{1}{2}$  gr.) as fresh 10% solution 1 M or 1 V. (2) Paraldehyde, 5-15 ml (1-4 dr.) orally in cracked ice with milk, fruit juice, or whisky, or 5-30 ml (1-8 dr.) rectally in an equal quantity of vegetable or mineral oil, or 5-10 ml 1 M, into the buttocks. (3) Calcium gluconate, 10%, 10-20 ml 1 V (for tetany).

2. CNS depression - Use stimulant drugs as for respiratory depression.

D. Agranulocytosis - In the presence of fever, sore throat, or other signs of infection, give penicillin, one million units daily, or a broad-spectrum antibiotic in maximum doses until infection is controlled. Give repeated fresh blood transfusions.

E. Methemoglobinemia - Give 100% oxygen by mask, and methylene blue, 5-25 ml of 1% solution slowly 1 V.

## TREATMENT OF COMMON SPECIFIC POISONINGS (ALPHABETICAL ORDER)

**ACIDS, CORROSIVE**

The strong mineral acids exert primarily a local corrosive effect on the skin or mucous membranes. In severe burns circulatory collapse may result. Symptoms include severe pain in the throat and upper gastrointestinal tract, marked thirst, bloody vomitus, difficulty in swallowing, breathing, and speaking, discoloration and destruction of skin and mucous membranes in and around the mouth, and shock.

The MLD is 1 ml of concentrated acid.

Inhalation of volatile acids, fumes, or gases such as fluorine, bromine, or iodine cause severe irritation of the throat and chest with paroxysmal coughing and inhibition of respiration, followed by pulmonary edema.

**Treatment.**

A. Ingested - Dilute immediately by giving large quantities of milk or water to drink, give beaten eggs (at least 12) as a demulcent. Gastric lavage should be performed within the first hour after exposure only. (Perforation may occur if passage of a tube is attempted after one hour.) Pass a Levin tube gently and lavage with 2-4 L of warm tap water. Do not give chemical antidotes.

Relieve pain and treat shock.

**B Skin Contact** Flood with water for 15 minutes Use no chemical antidotes the heat of the reaction may cause additional injury Relieve pain and treat shock

**C Eye Contact** Flood with water for 5 minutes holding the eyelids open Relieve pain

**D Inhalation** Remove from further exposure to fumes or gas Treat pulmonary edema

Lewis, G K Chemical burns Am J Surg 98 928-37, 1959

Steigmann, F., & R A Dolehide Corrosive (acid) gastritis management of early and late cases New England J Med 254 981-5, 1956

## ALCOROL, ETHYL

The principal manifestation of ethyl alcohol poisoning is CNS depression and mucous membrane irritation with nausea and vomiting Other manifestations include cerebral edema with severe headache and fever to 40.6-42.2° C (105-108°F)

Differentiate from barbiturate or paraldehyde poisoning head injury mental disorders and insulin hypoglycemia

The MLD is 300 ml

### Treatment of Acute Alcoholic Intoxication

**A Emergency Measures** Remove unabsorbed alcohol by gastric lavage with tap water Instill 4 Gm (60 gr) of sodium bicarbonate

**B General Measures** (Similar to those for barbiturate poisoning)

1 Maintain the airway and keep the patient warm

2 Give strong coffee orally or rectally or give caffeine and sodium benzoate 0.5 Gm (7½ gr) 1 M, no more frequently than once every 3-4 hours for 3-4 doses

3 If the patient is comatose and areflexic treat as for barbiturate poisoning (see p 780)

4 For nausea, vomiting and intractable retching prochlorperazine (Compazine®) 10 mg may be administered slowly deeply 1 M It may be repeated in 4-6 hours or the oral route may then be used in doses of 10-15 mg every 4-6 hours

5 In acute alcoholic mania administer paraldehyde 15 ml (4 dr) orally or rectally every 3-8 hours until mania has subsided Two

ml may be administered deeply 1 M, avoiding nerve trunks Sloughs occur, but only rarely

Cummins, L H Hypoglycemia and convulsions in children following alcohol ingestion J Pediat 58 23-6, 1961

Tavel, M E A new look at an old syndrome delirium tremens (editorial) Arch Int Med 109 129-33, 1962

## ALCOHOL, METHYL

Methyl alcohol is a mucous membrane irritant and CNS depressant which has an affinity for the optic nerve Its end-products cause a metabolic acidosis The MLD is 30-60 ml (1-2 oz) Symptoms include headache abdominal pain dyspnea nausea vomiting and blindness Examination reveals flush or cyanosis excitement or depression delirium coma and convulsions

### Treatment

Lavage well with 1-2% sodium bicarbonate solution Keep the patient in a dark room Check CO<sub>2</sub> combining power Give I V fluids to combat metabolic acidosis and sodium bicarbonate 5-15 Gm (¼-½ oz) orally every 2-3 hours Give ethyl alcohol 100 proof (50%) 3-20 ml orally every 2-4 hours for 3-4 days to block the metabolism of methyl alcohol until it is excreted

Austin, W H, Lape C P, & H N Burnham Treatment of methanol intoxication by hemodialysis New England J Med 265 334, 1961

## ALKALIES

The strong alkalies are common ingredients of household cleaning compounds and may be detected by their "soapy" texture They exert a local corrosive effect on mucous membranes and may produce circulatory failure Symptoms include burning pain in the upper gastrointestinal tract nausea vomiting and difficulty in swallowing and breathing Examination reveals destruction and edema of the affected skin and mucous membranes and bloody vomitus and stools

The MLD is 1 Gm (15 gr)

**Treatment.**

A. Ingested. Dilute immediately with 2 L. of water or milk, and allow the patient to vomit. Follow with 500 ml. of dilute vinegar (one part vinegar to 6 parts water) or fruit juice. Gastric lavage should be performed within the first hour only. (Perforation may occur if passage of a tube is attempted after one hour.) Gently pass a Levin tube and lavage with 2-4 L. of water or dilute vinegar, using 200 ml. portions and removing as much as possible of the liquid each time.

Relieve pain and treat shock.

Corticosteroids (see p. 583) have been reported to be of marked value in prevention of esophageal strictures or stenosis. The suggested dose is prednisone, 10 mg. q. i. d. for about 2 weeks.

B. Skin Contact. Wash with running water until the skin no longer feels soapy. Relieve pain and treat shock.

C. Eye Contact. Wash with water continuously for 15 minutes, holding the lids open. Relieve pain.

Csörver, G., Sealy, W., & M. Dillon, Jr.  
Management of alkali burns of the esophagus. *J.A.M.A.* 160 1447-50, 1956

**ANTICOAGULANTS**

Bishydroxycoumarin, ethyl biscoumatate, phenindione, and warfarin are used medically to inhibit the clotting mechanism. Abnormal bleeding occurs only after prolonged administration. The MLD of bishydroxycoumarin and warfarin is 0.1 Gm. (1½ gr.), of phenindione, 0.2 Gm. (3 gr.); of ethyl biscoumatate 0.6 Gm. (10 gr.). These compounds inhibit prothrombin formation in the liver and increase capillary fragility. The pathologic findings consist of numerous gross and microscopic hemorrhages.

**Clinical Findings.**

A. Symptoms and Signs. The principal manifestation of poisoning with the anticoagulants is bleeding: hemoptysis, hematuria, bloody stools, hemorrhages into organs, widespread bruising, and bleeding into joint spaces. Phenindione may also cause jaundice, hepatomegaly, skin rash, and agranulocytosis.

B. Laboratory Findings. The prothrombin concentration is lowered after administration

of coumarin and indandione anticoagulants. Gross or microscopic hematuria may be present. The RBC may also be reduced. WBC may be decreased after phenindione administration.

**Treatment.**

A. Emergency Measures. Discontinue the drug at the first sign of bleeding. If ingestion of more than 10 times the daily therapeutic dose is discovered within 2 hours, remove by gastric lavage and catharsis.

B. General Measures. Give menadiol sodium diphosphate, 75 mg. I. M., 1-3 times daily. For more rapid effect, give 10-50 mg. of phytonadione (Mephyton®) I. V., as the diluted emulsion. Give transfusions of fresh blood or plasma if hemorrhage is severe. Absolute bed rest must be maintained to prevent further hemorrhages.

Beamish, R. E., & N. D. McCreath. Intestinal bleed from anticoagulants, *Lancet* 2 380-2, 1961

**ANTIHISTAMINES**

Many antihistamines are sold both over the counter and by prescription for the treatment of allergies and colds and as hypnotics. Some are also used as motion sickness and psychotherapeutic remedies.

At least 20 fatalities due to antihistamine poisoning have been reported.

Antihistaminic drugs in toxic doses produce a complex of CNS excitatory and depressant effects. The pathologic findings are not characteristic. Cerebral and kidney damage have been observed at autopsy.

**Clinical Findings.**

The principal manifestation of poisoning with these drugs is convulsions or coma.

A. Acute Poisoning. Therapeutic doses cause a high incidence of toxic reactions, including drowsiness, dryness of the mouth, headache, nausea, tachycardia, visual disturbance, bowel dysfunction, tinnitus, skin rash, urinary retention, and nervousness. Larger doses may have a depressant effect, with drowsiness, disorientation, staggering gait, hallucinations, stupor, and coma, or an excitant effect, with hyperreflexia, tremors, tachycardia, excitement, nystagmus, fever,

and convulsions. The same drug may cause different types of manifestations in different patients, or a combination of depressant and excitant effects may occur in the same patient.

**B Chronic Poisoning** Tripeleennamine, methapyrilene, and promethazine have caused agranulocytosis. Aplastic anemia has been reported after administration of tripeleennamine and pyrilamine.

**C. Laboratory Findings** The WBC may be low, granulocytes may be absent or low. Bone marrow may show aplasia.

#### Treatment.

##### A Acute Poisoning

1. Emergency measures - Delay absorption by giving tap water, milk, or universal antidote and then remove by gastric lavage or emesis with tap water followed by catharsis. If coma and respiratory depression are present, use resuscitative measures. Caution: Do not use stimulants. Maintain normal BP by giving levarterenol (Levophed®), 4-18 ml of 0.2% solution per L. of normal saline by slow I.V. drip.

2. General measures - Control convulsions by cautious ether administration or I.V. barbiturates.

3. Special problems - Treat agranulocytosis.

**B. Chronic Poisoning** Discontinue drug at onset of symptoms.

##### Acute Fatal Doses of Antihistamines

The acute fatal dose of the antihistamines is usually estimated to be about 25-50 mg/Kg. The estimated fatal dose of perazopyrilamine (Dimetane®), chlorpheniramine (Chlor-Trimeton®), and diphenylpyraline (Difen®) is 5-10 mg/Kg. Actual fatalities have been reported following ingestion of Antallergan® 800 mg (50 mg/Kg), diphenhydramine (Benadryl®), 400 mg (40 mg/Kg), methapyrilene (Seminon®, Thienylene®), 100 mg (10 mg/Kg), and pyrilamine (Neo-Antergan®), 1 Gm (40 mg/Kg).

Reichelderfer, T., & others. Treatment of acute benadryl intoxication with severe central nervous system changes and recovery. *J. Pediatr* 46:303-7, 1955.

## ARSENIC

Arsenic is found in pesticides and industrial chemicals. Symptoms of poisoning usually appear within one hour after ingestion but may be delayed as long as 12 hours. They include abdominal pain, difficulty in swallowing, persistent vomiting, diarrhea, urinary suppression, and skeletal muscle cramps. Later findings are severe thirst and shock.

The MLD is 0.1 Gm (1 1/2 gr.)

#### Treatment.

A. Emergency Measures. Induce vomiting with the finger, or give 1 Tbsp table salt or 1 tsp powdered mustard in water. Follow with 500 ml of milk. Lavage with 2-4 L of warm tap water. 200 ml at a time. Treat shock.

B. Antidote. Give dimercaprol injection (BAL), 10% solution in oil. The side effects include nausea, vomiting, headache, generalized aches, and burning sensations around the head and face. These usually subside in 30 minutes. Barbiturates have been recommended for severe side effects.

1. Severe poisoning - Give I.M. 3 mg/Kg for each injection (1.8 ml/60 Kg).

First and second days - One injection every 4 hours day and night.

Third day - One injection every 6 hours for 4 doses.

Fourth and subsequent days - One injection b.i.d. for 10 days or until recovery is complete.

2. Mild poisoning - 2.5 mg/Kg/dose (1.5 ml/60 Kg).

First day - One injection every 4 hours for 4 doses.

Second day - One injection every 4 hours for 4 doses.

Third day - One injection b.i.d.

Fourth and subsequent days - One injection once or twice a day for 10 days or until recovery is complete.

C. General Measures. Relieve pain and treat diarrhea.

Bowen, A.L., Lewis, T.L.T., & W.R. Edwards. Acute arsenical poisoning due to acetarsol pessaries. *Brit. M.J.* 1 1282, 1961.

## BARBITURATES

The barbiturates are among the most common offenders in accidental as well as suicidal poisoning. Obtain data on dosage and time of ingestion from the patient, relatives, friends, or attending physician when possible.

Symptoms of mild poisoning consist of drowsiness, mental confusion, and headache. There may be euphoria or irritability. Moderate or severe poisoning causes delirium, stupor, shallow and slow respirations, circulatory collapse, cold clammy skin, cyanosis, pulmonary edema, dilated and nonreacting pupils, hyporeflexia, coma, and death.

The MLD is 0.5-2 Gm (7 1/2-30 gr.)

### Treatment.

**Note:** The critical factor in the management of barbiturate poisoning is constant medical and nursing attendance to maintain physiologic responses until the danger of respiratory failure and circulatory depression has passed.

**A Mild Poisoning.** Induce vomiting and give symptomatic and supportive nursing care. Keep the patient under observation until he is out of danger. Place suicidal patients under psychiatric care.

**B Moderate or Marked Poisoning.** Most patients will survive even days of unconsciousness if the airway is kept open (usually requires tracheostomy) and if artificial respiration is maintained with a tank respirator, IPPB, or other mechanical ventilating apparatus. The patient should be hospitalized, and antishock measures instituted (see p. 2). Examine the patient and record the following at intervals of 1-4 hours (or oftener if the patient's condition is very poor): temperature, pulse, respiration and BP, mental status or state of consciousness, skin color (cyanosis or pallor), lung bases (pulmonary edema), reflexes (corneal, pupillary, gag, patellar), and sensation (response to pain).

**1 Airway.** Aspirate mucus, pull tongue forward, and insert oropharyngeal airway. Intratracheal or tracheostomy intubation may be advisable.

**2 Lavage** with 2-4 L. of warm tap water, preferably containing 4-5 Tbsp of universal antidote per L. This is of doubtful value and may be dangerous if done more than 6 hours after ingestion. **Caution:** The danger of aspiration pneumonia is great in stuporous or comatose patients.

**3 Alkalinization** of the urine increases excretion.

**4 Insert** an indwelling catheter and save all urine in the first 48 hours for toxicologic studies.

**5 Parenteral fluids.** If cardiac failure is absent and renal function is adequate, give 1 L. of 0.45% sodium chloride solution and 1-2 L. of 5% dextrose solution I.V. daily to maintain a urine output of 1-1.5 L./day. Unless fluid loss has been excessive, do not give more than 2-3 L. of fluid during the first 24 hours. In the event of shock, give plasma or a vasopressor agent such as levarterenol (Levophed®), 8-32 mg./L. in isotonic sodium chloride solution at a rate of 20-40 drops/minute in order to maintain a satisfactory BP.

**6 CNS stimulants** (analeptics or convulsant drugs) - Picrotoxin, pentylenetetrazol, amphetamine, ephedrine, methamphetamine, strychnine, and bemegride (Megimide®) have been used but they are not true antidotes. Their place in the treatment of barbiturate poisoning is uncertain. They do not shorten the duration of effect of poisoning, and after their stimulant effects have passed the depression may be even more severe.

**7 The artificial kidney or peritoneal dialysis** is indicated in severe cases when the necessary equipment and trained personnel are available.

Balagot, R., Tsuji, H., & M. Sadovs: Use of an osmotic diuretic - THAM - in treatment of barbiturate poisoning. *J.A.M.A.* 178:1000-4, 1961.

Böttiger, L.E., & J. Östman: Treatment of barbiturate intoxication, with a survey of 311 cases. *Acta med scandinav.* 165:437-44, 1959.

Hahn, F.: *Analeptics*. *Pharmacol. Rev.* 12:447-530, 1960.

## BELLADONNA DERIVATIVES (Atropine & Scopolamine)

The belladonna alkaloids are parasympathetic depressants with variable CNS effects. The patient complains of dryness of the mouth, thirst, difficulty in swallowing, and blurring of vision. The physical signs include dilated pupils, flushed skin, tachycardia, fever, delirium, delusions, paralysis, stupor, and a rash on the face, neck, and upper trunk.

The MLD of atropine is 2-10 mg (1/30-1/6 gr.)

### Treatment.

Remove the poison by lavage and catharsis, and counteract excitement.

**A Emergency Measures** induce vomiting and lavage with 2-4 L. of water preferably containing 4 heaping Tbsp. of universal antidiote per L. Follow lavage with sodium sulfate 30 Gm (1 oz.) in 200 ml. of water

**B General Measures** Short acting barbiturates such as secobarbital (Seconal) 0.1 Gm (1 1/2 gr.) by mouth may be used if the patient is excitable. Treat respiratory difficulty as for barbiturate poisoning (see p. 780). Alcohol sponge baths are indicated to control high temperatures. Maintain BP.

**Hoefnagel D** Toxic effects of atropine and homatropine eyedrops in children. New England J Med 264:168-71, 1961

### BROMIDES

Bromides are CNS depressants frequently found in hypnotic and anticonvulsant preparations. Acute poisoning is rare. The symptoms include anorexia, constipation, drowsiness, apathy and hallucinations. The physical examination reveals dermatitis, conjunctivitis, foul breath, furred tongue, sordes, unequal pupils, stasis, abnormal reflexes (often bizarre), toxic psychosis, delirium and coma. The MLD is 10 Gm (1/3 oz.) or more.

#### Treatment

**A Emergency Measures** Lavage copiously with saline to remove unabsorbed bromides and later to remove those excreted into the stomach. Follow with sodium sulfate 30 Gm (1 oz.) in 200 ml. of water for catharsis.

**B General Measures** Give sodium chloride in addition to the regular dietary salt intake (1) 1000 ml. of physiologic saline I.V. or rectally once or twice daily or (2) 1-2 Gm (15-30 gr.) as salt tablets every 4 hours orally. Continue until the blood bromide level is below 50 mg./100 ml.

Force fluids to 4 L. daily.

Diuretics will aid excretion of bromide.

**Green D** Bromide intoxication. Survey of 15 years' experience at S.U.I. Hospitals. Iowa State M Soc J 51:189-94, 1961

### CARBON MONOXIDE

Carbon monoxide poisoning resulting from the use of unvented gas or coal burning heaters is an important cause of accidental death. Voluntary inhalation of carbon monoxide in exhaust fumes is often used for suicidal purposes. The gas exerts its toxic effect by combining with hemoglobin to form a relatively stable compound (carboxyhemoglobin) which secondarily causes tissue anoxia. Manifestations are headache, faintness, giddiness, tinny vomiting, cherry red skin, vertigo, loss of memory, fainting, collapse, paralysis and unconsciousness.

When blood containing carboxyhemoglobin is boiled or when it is shaken with 1-2 volumes of sodium hydroxide, it remains red. Normal blood becomes black or dark brown.

#### Treatment

**Remove the patient from the toxic atmosphere.** Loosen his clothing and keep him warm and at rest. Give artificial or resuscitation with 100% oxygen for at least one hour. Give 50 ml. of 50% glucose I.V. for cerebral edema. p.r.n. Maintain body warmth and BP.

**Katz M** Carbon monoxide asphyxia: a common clinical entity. Canad M A J 78:182-6, 1958

**Lorhan P H & H A Brookler** Carbon monoxide poisoning: management with hypothermia. Anesth & Analg 40:502-4, 1951

### CARBON TETRACHLORIDE

Carbon tetrachloride is a local irritant and protoplasmic poison which when ingested or inhaled may severely damage the heart, liver and kidneys. The effects are increased by ingestion of alcohol. Manifestations include headache, hiccup, nausea, vomiting, diarrhea, abdominal pain, drowsiness, visual disturbances, neuritis and intoxication. Early signs are jaundice, liver tenderness, oliguria and uremia. Nephrosis and cirrhosis may occur later.

The MLD is 3 ml.

#### Treatment

**A Emergency Measures** Remove the patient from exposure and keep him recumbent and warm. For poisoning due to ingestion, lavage copiously with tap water and give sodium sulfate 30 Gm (1 oz.) in 200 ml. of water.

**B. General Measures** Give inhalations of 100% oxygen by mask for one hour and artificial respiration if respirations are depressed. Treat cardiac, hepatic, and renal complications symptomatically. Do not give alcoholic beverages.

Dawborn, J., Ralson, M., & J. Weiden:  
Acute carbon tetrachloride poisoning.  
Transaminase and biopsy studies Brit.  
M J. 5250.493-4, 1961.

### CHLOROPHENOTHANE (DDT)

DDT is a CNS stimulant which can cause poisoning by ingestion, inhalation, or direct contact. The MLD is probably about 20 Gm (5 dr.) Few fatalities have been reported. Poisoning following ingestion of DDT solution is usually due to the organic solvent. The manifestations are tired and aching limbs, nervous irritability, mental sluggishness, muscle twitchings, convulsions and coma. The convulsive dose is approximately 20 Gm.

#### Treatment.

**A Emergency Measures** (Avoid epinephrine, which may cause ventricular fibrillation) Give universal antidote at once if available. Lavage with large quantities of warm tap water, and give sodium sulfate, 30 Gm (1 oz) in 200 ml of water as cathartic.

**B General Measures** Pentobarbital sodium, 0.1 Gm. (1 1/2 gr) orally, may be sufficient to calm the patient. For convulsions give amobarbital sodium (Amytal®) 0.25-0.5 Gm (3 3/4-7 1/2 gr) as fresh 10% solution slowly I.V. or 1 M. or calcium gluconate, 10%, 10 ml I.V. The diet should be high in carbohydrates and protein, with vitamin B supplementation to protect the liver.

Hayes, W., Durham, W.F., & C. Cueto, Jr.  
The effect of known repeated oral doses of chlorophenothane (DDT) in man. J.A.M.A. 162 890-7, 1956

### CYANIDES; HYDROCYANIC ACID (Prussic Acid, Rat Poison, Cyanogas®, Cyanogen)

Hydrocyanic acid and the cyanides cause death by inactivation of the respiratory enzyme, preventing utilization of oxygen by the tissues. The clinical combination of cyanosis, asphyxia, and the odor of bitter almonds on the breath is diagnostic. Respiration is first stimulated and later depressed. A marked drop in BP may occur.

The MLD is 0.05 Gm (3/4 gr)

#### Treatment.

**A Emergency Measures** Act quickly. Use nitrites to form methemoglobin, which combines with cyanide to form nontoxic cyanmethemoglobin. Then give thiosulfates to convert the cyanide released by dissociation of cyanmethemoglobin to thiocyanate.

1 Poisoning by inhalation - Place patient in open air in recumbent position. Remove contaminated clothing. Give artificial respiration.

2 Poisoning by ingestion - Induce vomiting immediately with a finger down the patient's throat. Do not wait until lavage tube has arrived, death may occur within a few minutes.

3 Give amyl nitrite inhalations for 15-30 seconds every 2 minutes.

**B Antidote** Give both of the following at once and repeat if symptoms recur: Sodium nitrite, 3%, 10-15 ml I.V., or 1%, 50 ml. I.V., taking 2-4 minutes to give injection; and sodium thiosulfate, 25%, 50 ml I.V.

**C General Measures** Combat shock and give 100% oxygen by forced ventilation.

Cope, C. Importance of oxygen in the treatment of cyanide poisoning. J.A.M.A. 175 1061-4, 1961.

Treatment of cyanide poisoning. Annotation. Lancet 1-1391, 1961.

### DIGITALIS

Because digitalis, digitoxin, and related drugs have a prolonged action, poisoning is most likely to occur when large doses are given to patients who have previously received digitalis drugs. Digitalizing doses should therefore be given only to patients who have not received digitalis for at least one week.



**Clinical Findings.**

The principal manifestations of digitalis poisoning are vomiting and irregular pulse. Other signs include anorexia, nausea, diarrhea, yellow vision, delirium, slow pulse, fall of BP, and ventricular fibrillation. The ECG may show lengthened P-R interval, heart block, ventricular extrasystoles, ventricular tachycardia, and a depressed ST segment.

The MLD of digitalis is 3 Gm. (45 gr.); of digitoxin, 3 mg. (1/20 gr.).

**Treatment.**

**A. Emergency Measures:** Delay absorption by giving tap water, milk, or universal antidote and then remove by gastric lavage or emesis followed by catharsis. Do not give epinephrine or other stimulants. These may induce ventricular fibrillation.

**B. General Measures:** Give potassium chloride, 2 Gm. (30 gr.) dissolved in water, every hour orally, or 0.3% in 5% dextrose slowly I.V., until the ECG shows improvement. If kidney function is impaired, serum potassium must be determined before potassium chloride is given.

Rodensky, P. L., & F. Wasserman: Observations on digitalis intoxication. Arch. Int. Med. 108:171-88, 1961.

### FLUORIDES SOLUBLE IN WATER (Insect Powders)

Symptoms include vomiting, diarrhea, salivation, shallow, rapid, and difficult respirations; convulsive seizures, rapid pulse, coma, and cyanosis. Interference with calcium metabolism causes severe damage to the vital centers and may result in death due to respiratory failure.

The MLD is 1 Gm. (15 gr.)

**Treatment.**

**A. Emergency Measures:** Lavage with lime water, 1% calcium chloride, calcium lactate, or calcium gluconate, or large quantities of milk to form insoluble calcium fluoride. Give calcium gluconate, 10%, 10-20 ml. I.V.; or calcium chloride, 5%, 10-20 ml. I.V. for convulsions. Give sodium sulfate, 30 Gm. (1 oz.). in 200 ml. of water as cathartic, and egg whites beaten in milk as demulcent.

**B. General Measures:** Treat shock and give supportive measures.

**Symposium:** The physiologic and hygienic aspects of the absorption of inorganic fluorides. Arch. Indust. H. 21:303-52, 1960

Peters, J. H.: Therapy of acute fluoride poisoning. Am. J. Med. Sc. 216:278-85, 1948.

### GASOLINE & RELATED COMPOUNDS

Gasoline poisoning may result from inhalation or ingestion but more severe symptoms result from inhalation because the CNS is more quickly reached by this route. Acute manifestations are vomiting, pulmonary edema, bronchial pneumonia, vertigo, muscular incoordination, weak and irregular pulse, twitchings, and convulsions. Chronic poisoning causes also headache, drowsiness, dim vision, cold and numb hands, weakness, loss of memory, loss of weight, tachycardia, mental dullness or confusion, sores in the mouth, dermatoses, and anemia.

The MLD is 10-50 ml

**Treatment.**

Remove the patient to fresh air, and lavage with salad oil or large amounts of warm saline (or both), taking extreme care to prevent aspiration. Give sodium sulfate, 30 Gm (1 oz.) in 200 ml. of water and follow with liquid petrolatum, 120 ml (4 oz.) Watch closely for 3-4 days for symptoms of respiratory involvement.

Ashkenazi, A. E., & S. E. Berman: Experimental kerosene poisoning in rats. Pediatrics 28:642-9, 1961

### IODINE

The clinical features of iodine poisoning include a characteristic stain of the mouth and odor of the breath, yellow or bluish vomitus, pain and burning in the pharynx and esophagus, marked thirst, diarrhea (stools may be bloody), weakness, dizziness, syncope, and convulsions.

The MLD is 2 Gm (30 gr.)

**Treatment.**

**A. Emergency Measures:** Give 15 Gm (1/2 oz.) cornstarch or flour in 500 ml. of water or, if available, 250 ml. of 1% sodium thiosulfate in water. Follow with an emetic.

or remove by lavage with sodium thiosulfate solution 1% and repeat until evidence of iodine has disappeared from the gastric contents. Then give demulcents e.g., milk or barley water.

**B General Measures** Treat systemic symptoms as indicated with stimulants or anticonvulsants.

Finkelstein, R., & M. Jacobi. Fatal iodine poisoning. A clinico-pathologic and experimental study. *Ann Int Med* 10:1283-96, 1937.

## LEAD

Lead poisoning may occur by ingestion or by inhalation of lead dust or fumes. Lead has a local astringent action and a general toxic effect. Poisoning is manifested by metallic taste, dry throat, thirst, abdominal colic, vomiting, diarrhea, constipation, headache, leg cramps, black stools (lead sulfide), oliguria, stupor, convulsions, palsies, and coma. Chronic lead poisoning causes variable involvement of the CNS, the blood-forming organs, and the gastrointestinal tract.

The MLD is 0.5 Gm (15 gr) of absorbed lead.

### Treatment

**A Acute Poisoning** Caution. Do not use dimercaprol (BAL).

1. Lavage with dilute sodium sulfate or magnesium sulfate solution to precipitate in soluble lead sulfate.

2. Treat symptomatically. Do not give narcotics. Treat colic with local heat, antispasmodics, and sedatives.

3. Calcium disodium edathamil (EDTA Versenate®) which forms a soluble unionizable lead complex which is excreted in the urine, has been used successfully in the treatment of lead poisoning. Give continuously I V (2% solution) or intermittently I M (20% solution containing 0.5% procaine) in a total dosage range of 10-50 mg/Kg/24 hours for a course of 5-7 days. The drug is nephrotoxic and should not be given in doses exceeding 5 Gm/24 hours. Rapid infusion and excessive volumes of sodium-containing solutions may aggravate the already increased intracranial pressure in cases of encephalopathy, especially in children. EDTA may be given orally 1 Gm qid.

4. Renal function and fluid and electrolyte requirements must be considered on an individual basis.

**B Chronic Poisoning** Remove permanently from exposure and give an adequate diet with vitamin supplements. Courses of EDTA as for acute poisoning may be employed especially when hematologic complications have occurred.

Brieger, H., & F. Rieders. Chronic lead and mercury poisoning: contemporary views on ancient occupational diseases. *J Chronic Dis* 9:177-84, 1959.

Greengard, J., & others. Lead encephalopathy in children. Intravenous use of urea in its management. *New England J Med* 264:1027-30, 1961.

## MERCURY

Mercury is a general protoplasmic poison. Acute poisoning (by ingestion or inhalation) is manifested by a metallic taste, salivation, thirst, a burning sensation in the throat, discoloration and edema of oral mucous membranes, abdominal pain, vomiting, bloody diarrhea, and shock. Chronic poisoning causes weakness, ataxia, intention tremors, irritability, depression, and muscle cramps.

The MLD is about 70 mg (1+ gr) of mercury bichloride.

### Treatment

**A Acute Poisoning** Gives whites of eggs beaten with water or skimmed milk as demulcent. dimercaprol (BAL) at once as for arsenic poisoning (see p. 779), and sodium sulfate, 30 Gm (1 oz) in 200 ml of water as cathartic. Maintain fluid output with 1000 ml of physiologic saline solution I V at once and repeat as necessary. Treat oliguria and anuria if it occurs (see p. 741).

**B Chronic Poisoning** Remove from exposure.

Brieger, H., & F. Rieders. Chronic lead and mercury poisoning: contemporary views on ancient occupational diseases. *J Chronic Dis* 9:177-84, 1959.

Matthes, F. T., & others. Acute poisoning associated with inhalation of mercury vapor. Report of 4 cases. *Pediatrics* 22:675-88, 1958.

# MORPHINE & OTHER NARCOTIC ANALGESICS

# MUSHROOMS

Morphine acts primarily on the CNS, causing depression and narcosis. The manifestations of poisoning with morphine and its derivatives, meperidine (Demerol®), and methadone (Dolophine®) are headache, nausea, excitement, depression, pin-point pupils, slow respirations, rapid and feeble pulse, shock, and coma.

The MLD is 65 mg (1 gr.) in susceptible individuals.

## Treatment.

As an antidote for overdosage, give nalorphine hydrochloride (Nalline®), 5-10 mg 1 V, or levallorphan (Lorfan®), 1 mg 1 V. If effective increase in pulmonary ventilation is not achieved with the first dose, the dose may be repeated every 15 minutes until respirations return to normal and the patient responds to stimuli.

Maintain adequate ventilation with artificial respiration, using oxygen if necessary. Lavage stomach well (prevent aspiration) with 1:2000 potassium permanganate solution at short intervals. Morphine is excreted into the stomach. Give sodium sulfate, 30 Gm (1 oz.) in 200 ml. of water as cathartic.

Bronstein, M., Yorburg, L., & B. Johnston: N-allylnormorphine in treatment of methorphinan (Dromoran®) hydrobromide poisoning. *J. A. M. A.* 151:908-10, 1953.

The *Amanita* genus of mushrooms accounts for almost all cases of fungus poisoning in the United States. *Amanita muscaria* poisoning, of rapid onset, responds promptly to atropine if treatment is given early. There is no specific antidote for the delayed type of mushroom poisoning due to *Amanita phalloides*, *A. brunneescens*, and *A. verna*, and the prognosis is usually poor (see chart on opposite page).

Buck, R. W.: Mushroom toxins. Brief review of literature. *New England J. Med.* 265:681-6, 1961.

Cann, H., & H. Verhulst: Mushroom poisoning. *J. Dis. Child.* 101:128-31, 1961.

## OXALIC ACID

Oxalic acid, a component of bleaching powder, is a powerful local irritant which precipitates ionized calcium. Poisoning is manifested by burning in the mouth and throat, violent abdominal pains, bloody vomitus, dyspnea, tremors, oliguria, and circulatory collapse.

The MLD is 4 Gm. (1 dr.).

## Treatment.

A Emergency Measures Give at once one of the following to precipitate as insoluble

Mushroom Poisoning

	<i>Amanita muscaria</i>	<i>Amanita phalloides</i> , <i>A. brunneescens</i> , <i>A. verna</i>
Pharmacologic action	Parasympathetic stimulation by muscarine (an alkaloid)	Direct toxic action on almost all cells, especially the liver, heart, and kidneys.
Onset	Sudden (1-2 hours)	Delayed (12-24 hours)
Symptoms and signs	Confusion, excitement, thirst, nausea and vomiting, diarrhea, wheezing, salivation, slow pulse, tremors, weakness, collapse, and even death	Confusion, depression, headache, convulsions, coma, nausea and vomiting, bloody vomitus and stools, painful enlargement of liver, jaundice, oliguria, pulmonary edema
Rationale of treatment	(1) Remove GI contents by emesis and lavage followed by catharsis (2) Antidote: Atropine sulfate, 1-2 mg ( $\frac{1}{60}$ - $\frac{1}{30}$ gr.) subcut. stat and repeat every 30 minutes p r n. Discontinue if signs of atropine poisoning appear (see p. 689). (3) Give barbiturate sedatives for excitement. (4) Force fluids by oral and parenteral routes. (5) Treat shock.	(1) Remove GI contents by emesis and lavage followed by catharsis. (2) Treat nonspecific parasympathetic autonomic effects with atropine sulfate, 1-2 mg ( $\frac{1}{60}$ - $\frac{1}{30}$ gr.) subcut at once and repeat every 30 minutes p r n. (3) Relieve pain with narcotics p r n. (4) "Protect" liver with 4-5 L. of 5% dextrose solution every 24 hours if renal function is adequate. (5) Treat shock.

calcium oxalate (1) Calcium lactate or other calcium salt, 30 Gm (1 oz) in 200 ml of water, (2) a glass of lime water, or (3) large amounts of milk. Lavage with potassium permanganate, 1:2000 solution and remove excess. Give whites of eggs beaten in milk as demulcent.

**B General Measures** Give calcium gluconate or calcium lactate, 10 ml of 10% solution I.V., and calcium orally, 1-2 Gm (15-30 gr), *q i d*. Institute supportive measures as required.

## PHENOLS & DERIVATIVES

The phenols are present in carbolic acid, lysol, cresol, and creosote. They are local corrosives and also have marked systemic effects on the nervous and circulatory systems. Manifestations include burning in the upper gastrointestinal tract, thirst, nausea and vomiting, erosions of mucous membranes, dark vomitus, oliguria, muscle spasms, circulatory collapse, and respiratory failure.

The MLD is 1.4 Gm (22 gr).

### Treatment.

**A Ingestion** Delay absorption by giving tap water, milk, or universal antidote and then remove by repeated gastric lavage with tap water or by inducing vomiting. Then give castor oil, 60 ml (2 oz) followed by sodium sulfate, 30 Gm (1 oz) in 200 ml of water. Do not give mineral oil and do not use alcohol for lavage. Give supportive measures as outlined on p 776.

**B External Burns** Wash with rubbing alcohol and then soap and water.

Deichman, W.: Local and systemic effects following skin contact with phenol. *J. Indust Hyg & Toxicol* 31:146-54, 1949.

## PHENOTHIAZINE TRANQUILIZERS (Chlorpromazine, Promazine, Prochlorperazine, Etc.)

Chlorpromazine and related drugs are synthetic chemicals derived in most instances from phenothiazine. They are used as antiemetics and psychic inhibitors, and as potentiators of analgesic and hypnotic drugs.

The acute fatal dose for these compounds appears to be above 50 mg/Kg. Fatal poisoning from ingestion of approximately 75 mg/Kg has been reported.

### Clinical Findings.

**A Symptoms and Signs** Minimum doses induce drowsiness and mild hypotension in as many as 50% of patients. Larger doses cause drowsiness, severe postural hypotension, tachycardia, dryness of the mouth, nausea, ataxia, anorexia, nasal congestion, fever, constipation, tremor, blurring of vision, stiffness of muscles, and coma. I.V. injection of solutions containing more than 25 mg/ml of these drugs causes thrombophlebitis and cellulitis in a small number of patients.

Prolonged administration may cause leukopenia or agranulocytosis, jaundice, and generalized maculopapular eruptions; overdosage causes a syndrome similar to paralysis agitans, with spasmodic contractions of the face and neck muscles, extensor rigidity of the back muscles, carpopedal spasm, motor restlessness, salivation, and convulsions.

### B Laboratory Findings

1 Liver function tests indicate the presence of obstructive jaundice.

2 Urine - Phenothiazine compounds in urine acidified with dilute nitric acid can be detected by the addition of a few drops of tincture of ferric chloride. A violet color results.

### Treatment

Remove overdoses by gastric lavage or emesis. For severe hypotension, levarterenol may be necessary (see p 4). Control convulsions with pentobarbital. Avoid other depressant drugs.

Give antiparkinsonism drugs in the presence of fever, sore throat, pulmonary congestion or other signs of infection; give penicillin, one million units daily, or a broad-spectrum antibiotic in maximum doses until infection is controlled. No measures have been helpful for jaundice other than discontinuing the drug.

## PHOSPHORUS, ORGANIC (Pesticide Sprays: Parathion, TEPP, Malathion, Thimet, Phosdrin, Systox, HETP, EPN, OMPA, Etc.)

Inhalation, skin absorption or ingestion of organic phosphorus causes marked depres-

sion of cholinesterase, resulting in continuous and excessive stimulation of the parasympathetic nervous system. Manifestations of acute poisoning appear within hours after exposure and include headache, sweating, salivation, lacrimation, vomiting, diarrhea, muscular twitchings, convulsions, dyspnea, and blurred vision. Contracted pupils with the above symptoms and signs and a history of exposure during the past 24 hours warrant therapy.

The MLD is 0.02-1 Gm (3-15 gr.)

#### Treatment.

**A Emergency Measures** If the material has been ingested, remove poison by inducing vomiting or gastric lavage with tap water. Counteract parasympathetic stimulation by giving atropine sulfate, 2 mg ( $\frac{1}{30}$  gr.) I M every 30 minutes until symptoms are relieved or signs of atropinization (blurred vision, dry mouth) appear. Repeat as necessary to maintain complete atropinization. As much as 12 mg ( $\frac{4}{5}$  gr.) of atropine has been given safely in the first 2 hours. Give pralidoxime, 1 Gm I V in aqueous solution and sodium sulfate, 30 Gm (1 oz.) in 200 ml of water orally.

**B General Measures** Give oxygen under positive pressure if pulmonary edema or respiratory difficulty appears. Prolonged artificial respiration may be necessary. Take a blood sample for determination of red cell cholinesterase levels. (This is of no practical value in immediate diagnosis or treatment of the acute episode but aids in confirmation of the diagnosis.)

Quinby, G., & G Clappison. Parathion poisoning. Arch Environ H 3 538-54, 1961

#### PHOSPHORUS, INORGANIC (Rat Paste, Fireworks, Matches)

Phosphorus poisoning may result from contact, ingestion or inhalation. Phosphorus is a local irritant and systemic toxin which acts on the liver, kidneys, muscles, bones, and cardiovascular system. Toxicity is manifested early by a garlic taste, pain in the upper gastrointestinal tract, vomiting and diarrhea. Other symptoms and signs are headache, pleuritis, extreme weakness, jaundice, oliguria, petechiae, prostration, and cardiovascular collapse.

The MLD is 50 mg ( $\frac{3}{4}$  gr.)

#### Treatment.

**A Emergency Measures** Lavage with one of the following: (1) copper sulfate, 1 1000 solution (1 Gm in 1 L. water) and repeat 3-4 times per hour until 5-10 L. of solution have been used, or (2) potassium permanganate, 1 2000 solution (1 Gm in 2 L. water), and repeat 3-4 times. Use tap water lavage or induce emesis if copper sulfate or potassium permanganate is not available. Give sodium sulfate, 30 Gm (1 oz.) in 200 ml of water, and liquid petrolatum, 120 ml (4 oz.) (No other oils may be used.) Give whites of eggs beaten in milk as demulcent.

**B General Measures** Observe carefully for several days and treat as for acute hepatitis if signs of jaundice or liver involvement appear.

Brewer, E., & R J Haggerty. Rat poisoning II Phosphorus. New England J Med, 258 147-8, 1958

#### SALICYLATE POISONING

Salicylate poisoning is most commonly caused by aspirin ingestion. Effects include acid-base disturbances, hypoprothrombinemia, and gastroenteritis. The acid-base disturbances are the most dangerous. Respiratory alkalosis appears first, followed by metabolic acidosis.

Salicylates stimulate the respiratory center, producing hyperpnea,  $\text{CO}_2$  loss, a falling serum  $\text{CO}_2$  content, and a normal or high arterial blood pH. This combination represents respiratory alkalosis. In an effort to compensate, the kidneys excrete increased amounts of bicarbonate, potassium, and sodium but retain chloride. The chief dangers during this stage are hypokalemia and dehydration. Salicylates also interfere with carbohydrate metabolism, which results in the formation of fixed acids, probably ketones.

When the patient is first seen, he may be in alkalosis or acidosis. Diagnosis and treatment are dependent upon determination of serum  $\text{CO}_2$  content, potassium, sodium and chloride, and arterial pH. The urine is unreliable as an indication of acidosis or alkalosis.

Salicylates are potent stimulators of metabolism, and hyperthermia may result.

The clinical picture includes a history of salicylate ingestion, hyperpnea, flushed face, hyperthermia, tinnitus, abdominal pain, vom-

iting dehydration spontaneous bleeding twitchings convulsions pulmonary edema uremia and coma Salicylates may give a false positive ketonuria and glycosuria or true ketonuria and glycosuria may be present

The MLD is 5-10 Gm (75-150 gr)

#### Treatment

**A Emergency Measures** Aspirate the gastric contents first without using additional fluids and then lavage with 2-4 L of warm tap water containing 4 heaping Tbsp of universal antidote per L

**B General Measures** Treat dehydration and alkalosis with physiologic saline solution and added potassium as indicated Treat acidosis with 20 ml /Kg of sixth molar sodium lactate given I V over a period of 2 hours or by the administration of sodium bicarbonate 0.4 Gm /Kg orally or I V every 2 hours The use of THAM (trihydroxymethylaminomethane) has also been suggested Discontinue if blood pH goes over 7.4 or if the urine becomes alkaline Maintenance of alkaline urine greatly speeds the excretion of salicylates Administer alkalinizing agents I V to infants with great caution Adjustment of sodium and potassium in fluids should be based on serum sodium and potassium determinations Serial ECG's may be of value in controlling hypokalemia (see p 34)

Vitamin K<sub>1</sub> (Mephyton®) 50 mg I V should be given once for hypoprothrombinemia Whole blood or platelet transfusion is recommended for thrombocytopenia Peritoneal dialysis or an artificial kidney may be life saving for critically ill patients with a high serum salicylate concentration or renal insufficiency

Friedman S B & J F Stocks Observations on the treatment of salicylism in children New England J Med 265 1237-41 1961  
Whitten C F Kesaree N M & J F Goodwin Managing salicylate poisoning in children Am J Dis Child 101 178 1961

### SILVER NITRATE

Silver nitrate is a protein precipitant Poisoning is manifested by nausea vomiting diarrhea bloody stools blue discoloration about the mouth and shock

The MLD is 10 Gm (1/3 oz)

#### Treatment

Lavage with saline solution to precipitate silver chloride Give whites of eggs beaten in milk as demulcent and sodium sulfate 30 Gm (1 oz) in 200 ml of water as cathartic Institute supportive measures

Dimercaprol (BAL) has not proved effective

### SNAKE (& GILA MONSTER) BITES

The venom of poisonous snakes and lizards may be predominantly neurotoxic or predominantly hemotoxic (cytolytic) Neurotoxins cause respiratory paralysis hemotoxins cause hemorrhage due to hemolysis and destruction of the endothelial lining of the blood vessels The manifestations are local pain thirst profuse perspiration nausea vomiting stimulation followed by depression local redness swelling extravasation of blood and collapse

#### Treatment

**A Emergency Measures** Immobilize the patient and the bitten part immediately Avoid manipulation of the bitten area use of tourniquet or incision Do not allow the patient to walk or run or take alcoholic beverages or stimulants Give specific antiserum subcut after testing for serum sensitivity with 0.02 ml of 1:100 dilution of antiserum in 0.9% saline (Follow printed instructions) Carry the patient to a car and transport him to a hospital or other medical facility for definitive treatment Maintain BP by giving blood transfusions or by continuous I V drip of levarterenol (see p 4) Cortisone (25 mg daily) will relieve symptoms temporarily but it does not reduce the mortality rate

**B General Measures** Give plenty of warm fluids Use barbiturates as necessary for sedation

Danzig L & G Abels Hemodialysis of acute renal failure following rattlesnake bite with recovery J A M A 175 136-7 1961

Efrati P & L Relf Clinical and pathological observations on 65 cases of viper bite in Israel Am J Trop Med 2 1085-1108 1953

Russell F Injuries by venomous animals in the U S J A M A 177 903-90 1961

Ya P M Guzman T & J Perry Jr Treatment of bites of North American pit vipers South M J 54 134-6 1961

## SPIDER BITES & SCORPION STINGS

The toxin of the less venomous species of spiders and scorpions causes only local pain, redness, and swelling. That of the more venomous species causes generalized muscular pains, convulsions, nausea and vomiting, variable CNS involvement, and collapse.

### Treatment.

**A. Emergency Measures** As for snake bite (see above). If absorption has occurred, give calcium gluconate, 10%, 10 ml I V or I.M., and repeat as necessary.

**B. General Measures** Hot baths are of value for relief of pain. For local pain with no systemic involvement apply cold compresses of sodium bicarbonate. Give adequate sedation and institute supportive measures as indicated. Corticotropin or the cortisones may be of value in severe cases.

Shaffer, J.: Stinging insects - a threat to life. J.A.M.A. 177 473-4, 1961.

## STRYCHNINE

Strychnine poisoning may result from ingestion or injection. The manifestations are convulsions, opisthotonos, dyspnea, foaming at the mouth, and asphyxia.

### Treatment.

**A. Emergency Measures** Keep the patient quiet in a darkened room. Give amobarbital sodium (Amytal<sup>®</sup>) or an equivalent barbiturate sedative, 0.5 Gm. (7½ gr.) at once in 10-20 ml. of water slowly I.V. If smobarbital for injection is not available, give the drug orally in doses up to 5 times the hypnotic dose. Repeat in 30 minutes if necessary. Give artificial respiration and oxygen during convulsions. If possible, lavage gently with potassium permanganate solution before symptoms appear. Do not lavage after twitching or convulsions have appeared.

**B. General Measures** Inhalation of ether or chloroform may be used to quiet the patient. Give charcoal or tannic acid in water, or strong tea.

## WASP, BEE, YELLOW JACKET, & HORNET STINGS

Stings of these common insects, although locally painful, usually cause only mild symptoms of brief duration. Local cold compresses, application of baking soda solution, and oral salicylates or antihistamines are sufficient treatment. Multiple stings may cause a shock-like reaction with hemoglobinuria. Sensitive individuals may develop an acute allergic or even fatal anaphylactic response after a single sting.

### Treatment.

**A. Emergency Measures** Give epinephrine hydrochloride, 1:1000 solution, 0.2-0.5 ml subcut or I.M., and then diphenhydramine hydrochloride (Benadryl<sup>®</sup>), 5-20 mg. slowly I.V. Treat shock.

**B. General Measures** Corticotropin (ACTH) or the cortisones I.M. may be necessary to support shock therapy.

## TREATMENT OF LESS COMMON SPECIFIC POISONINGS (ALPHABETICAL ORDER)

### Acetaldehyde. (Industrial.)

Inhalation of acetaldehyde vapors causes severe irritation of mucous membranes with coughing, pulmonary edema, followed by narcosis. Ingestion causes narcosis and respiratory failure. The MLD in adults is about 5 Gm (75 gr.).

Remove from exposure or remove ingested poison by gastric lavage or emesis followed by catharsis. Give oxygen for respiratory difficulty. Treat pulmonary edema.

### Acetophenetidin & Acetanilid. (Analgesics.)

Acute poisoning is similar to that due to salicylates. Prolonged administration leads to renal impairment, cyanosis, hemolytic anemia, and skin eruptions. The MLD is 5-20 Gm. (75-300 gr.).

Treat as for salicylate poisoning. Treat methemoglobinemia by giving methylene blue, 5-25 ml. of 1% solution slowly I.V.

### Aconite. (Liniment.)

Manifestations are burning followed by numbness and tingling of the mouth, throat, and hands, blurred vision, weak pulse, fall of

BP shallow respirations convulsions and respiratory or cardiac failure The MLD is 1 Gm (15 gr) of aconite or 2 mg (1/30 gr) of aconitine

Remove ingested poison by gastric lavage or emesis followed by catharsis Give artificial respiration or oxygen as necessary Give digitals to counteract cardiac depression Treat convulsions Give atropine 1 mg (1/60 gr) to prevent vagal slowing of the heart

#### Akee (Tree)

Manifestations are abdominal discomfort vomiting convulsions coma hypothermia and fall of BP Jaundice may appear during the recovery phase

Remove ingested akee by gastric lavage or emesis followed by catharsis Control convulsions Give carbohydrates as 5% glucose 1 V or as sugar dissolved in fruit juice orally to protect from liver damage

#### Aminopyrine, Antipyrine, Phenylbutazone (Analgesics)

Manifestations are dizziness cyanosis coma and convulsions Prolonged administration causes epigastric pain urticaria leukopenia liver damage exfoliative dermatitis gastric or duodenal erosion adrenal necrosis The MLD is 5.30 Gm (1/4 oz)

Treat acute poisoning as for salicylates Treat chronic poisoning by discontinuing drug

#### Anilins (Industrial)

Manifestations are cyanosis shallow respirations fall of BP convulsions and coma Blood methemoglobin as determined photometrically may reach 60% or more of total hemoglobin The MLD is 1 Gm (15 gr)

Remove aniline from skin by washing thoroughly with soap and water or if ingested remove by emesis gastric lavage and catharsis Give fluids and oxygen if respiration is shallow or if there is evidence of air hunger As antidote for methemoglobinemia give methylene blue 10-50 ml of 1% solution I V

#### Antimony (Paint)

Manifestations are severe diarrhea with mucus followed by blood hemorrhagic nephritis and hepatitis The MLD is 100 mg (1 1/2 gr)

Remove ingested poison by gastric lavage emesis and catharsis Treat as for arsenic poisoning

#### Antineoplastic Agents

Manifestations are leukopenia thrombocytopenia nausea and anorexia

Give blood transfusions For aminopterin and methotrexate poisoning give leucovorin calcium 3-6 mg I M /day

#### Aralne (Industrial)

Manifestations are pyrexia cough abdominal pain hemolytic anemia hemoglobinuria anuria methemoglobinemia and diarrhea

Alkalinize urine as for fava bean poisoning Give blood transfusions if anemia is severe Treat anuria

#### Aspidium (Anthelmintic)

Manifestations are progressive vomiting colored or blurred vision tremors convulsions and respiratory failure The urine may show protein red cells and casts Jaundice and blindness may complicate recovery from nonfatal poisoning The MLD is 4 Gm (60 gr)

Treat as for chenopodium poisoning

#### Barium (Rodenticide)

Manifestations are tightness of the muscles of the face and neck fibrillary muscular tremors weakness difficulty in breathing irregularity of the heart convulsions and cardiac and respiratory failure The MLD is 1 Gm (15 gr)

Give 10 ml of 10% sodium sulfate slowly I V and repeat every 15 minutes until symptoms subside -Give 30 Gm (1 oz) sodium sulfate in 200 ml of water orally or by gastric tube and repeat in one hour

#### Benzene (Paint thinner)

Manifestations are visual blurring tremors shallow and rapid respiration ventricular irregularities unconsciousness and convulsions Repeated exposure results in anemia and abnormal bleeding The MAC is 35 p p m

Remove patient from contaminated air and give artificial respiration with oxygen Treat ingested poison as for gasoline poisoning

#### Beryllium (Industrial)

Manifestations include acute pneumonitis chest pain bronchial spasm fever dyspnea cough and cyanosis Right heart failure may occur Pulmonary granulomatosis with weight loss and marked dyspnea may occur years after initial exposure X ray examination reveals diffuse increase in density of the lung fields or snowstorm appearance No degree of exposure is safe

Place the patient at complete bed rest and administer 60% oxygen by mask for cyanosis EDTA has been suggested (see p 784) The administration of cortisone or related drugs gives symptomatic relief but is not curative



**Bismuth Compounds. (Antitreponema.)**

Manifestations are skin eruptions, liver damage, anuria, cardiovascular collapse, proteinuria, hematuria, and liver function impairment. The MLD is 0.5 Gm. (7½ gr.).

Give dimercaprol (BAL) (see p. 779); and atropine, 1 mg. (¼60 gr.) subcut., to relieve gastrointestinal discomfort. Give fluids, 2-4 L. daily, if kidney function is not impaired. Treat anuria.

**Bleaching Solutions. (Household.)**

Clorox®, Purex®, Sani-Clor®, etc., cause irritation and corrosion of mucous membranes with edema of the pharynx and larynx. Perforation of the esophagus or stomach is rare. The MLD is 15 ml. (½ oz.).

Remove ingested solution by gastric lavage or emesis, using a solution of sodium bicarbonate, 30-50 Gm./L., or milk. After emesis or lavage, give a cathartic consisting of sodium sulfate, 30 Gm. (1 oz.), and sodium bicarbonate, 10 Gm. (¼3 oz.), in 250 ml. of milk or water. Caution: Do not use acid antidotes. Treat as for sodium hydroxide poisoning.

**Boric Acid. (Antiseptic.)**

Manifestations from ingestion or skin application are fever, anuria, and flushing of the skin followed by desquamation, lethargy, and convulsions. The MLD is 5-15 Gm. (75-225 gr.).

Remove ingested boric acid by emesis or gastric lavage followed by catharsis. Maintain urine output by giving liquids orally or, in the presence of vomiting, by giving 5% dextrose I.V. Control convulsions by the cautious administration of ether. Remove circulating boric acid by peritoneal dialysis or with an artificial kidney. Treat anuria as for mercury poisoning.

**Bromates. (Cold wave neutralizer.)**

Manifestations are vomiting, abdominal pain, oliguria, coma, convulsions, fall of BP, hematuria, and proteinuria. The MLD is 4 Gm. (60 gr.).

Remove poison by gastric lavage, emesis, and catharsis. Give sodium thiosulfate, 1-5 Gm. I.V. as a 10% solution. Treat shock by administration of repeated small blood transfusions.

**Cadmium. (Metal plating.)**

Ingestion causes diarrhea, vomiting, muscular aches, salivatory, and abdominal pain. Inhalation causes shortness of breath, pain in the chest, foamy or bloody sputum, muscular aches. Chronic exposure produces, in addition, anemia, and x-ray examination indicates

lung consolidation. A sulfosalicylic acid precipitable protein is present in the urine. The MLD is about 10 mg. (¼6 gr.).

Treat pulmonary edema and give calcium edathamil (see p. 784). Remove ingested poison by emesis or gastric lavage followed by catharsis.

**Caffeine, Aminophylline. (Stimulants.)**

Manifestations are sudden collapse and cardiac arrest within 1-2 minutes after I.V. or rectal administration, and convulsions. The MLD is 1 Gm. (15 gr.).

Give oxygen by artificial respiration with forced ventilation, maintain BP, remove rectally administered aminophylline by enema, and control convulsions as for strychnine poisoning.

**Camphor. (Stimulant.)**

Manifestations are a feeling of tension, dizziness, irrational behavior, rigidity, tachycardia, twitching of the facial muscles, and generalized convulsions. The MLD is 1 Gm. (15 gr.).

Remove ingested poison by gastric lavage or emesis followed by catharsis. Control convulsions.

**Cantharidin. (Irritant.)**

Manifestations are severe vomiting, diarrhea, fall of BP, hematuria, and death in respiratory failure or uremia. The MLD is 10 mg (¼6 gr.).

Remove ingested poison by gastric lavage or emesis followed by catharsis. Treat cardiovascular collapse by blood transfusions, I.V. saline, and levarterenol. Treat anuria.

**Caster Beans.**

Manifestations are vomiting, diarrhea, severe abdominal pain, cyanosis, circulatory collapse, and oliguria. Urine may show protein, casts, red blood cells, and hemoglobin. The MLD is one bean.

Remove ingested beans by gastric lavage or emesis followed by catharsis. Maintain BP by blood transfusions. Alkalinize urine by giving 5-15 Gm. of sodium bicarbonate daily to prevent precipitation of hemoglobin or hemoglobin products in the kidneys. Treat anuria.

**Cationic Detergents (Zephiran®, Diaperene®, Pbenmerol®). (Antiseptics.)**

Manifestations are severe vomiting, collapse, convulsions, and death within 1-4 hours. The MLD is 1-3 Gm. (15-45 gr.).

Remove unabsorbed detergent by gastric lavage or emesis followed by catharsis. Ordinary face soap is an effective antidote for unabsorbed cationic detergent.

**Chloramine-T, (Disinfectant.)**

Manifestations are cyanosis, frothing at the mouth, and respiratory failure within a few minutes to one hour after ingestion. The MLD is 0.5 Gm. (7½ gr.).

Remove ingested chloramine-T by gastric lavage or emesis followed by catharsis. Give antidotes as for cyanide poisoning.

**Chlorates. (Disinfectant)**

Manifestations are cyanosis, hemolysis, anuria, and convulsions. The MLD is 15 Gm. (½ oz.). Laboratory findings include methemoglobinemia, anemia of the hemolytic type, and elevation of serum potassium.

Remove ingested chlorate by gastric lavage or emesis followed by catharsis. Treat methemoglobinemia with methylene blue. Force fluids to 2-4 L. daily to remove chlorate if urine output is adequate.

**Chlorinated Hydrocarbons.**

For volatile chlorinated hydrocarbons see Carbon Tetrachloride, p 781, for nonvolatile chlorinated hydrocarbons, see Chlorophenothane (DDT), p 782.

**Chlorinated Naphthalene. (Insulator)**

The principal manifestation is a papular, acneiform eruption which progresses to pustule formation. Jaundice, enlargement of the liver, and weakness also occur. Impairment of hepatic cell function is revealed by appropriate tests.

Treat liver damage as outlined under carbon tetrachloride poisoning.

**Chromium & Chromate. (Rustproofing)**

Ingestion causes abdominal pain, vomiting, shock, and oliguria or anuria. Skin contact leads to incapacitating eczematous dermatitis and ulceration. Ulceration and perforation of the nasal septum also occur. Acute hepatitis has been observed. Examination of the urine reveals proteinuria and hematuria. The MLD of soluble chromate is 5 Gm. (75 gr.).

Remove ingested chromate by gastric lavage, emesis, and catharsis. Treat oliguria and liver damage.

**Cinchophen & Neocinchophen. (Analgesics)**

Acute poisoning is similar to that due to the salicylates. Prolonged administration leads to jaundice, anorexia, abdominal discomfort and painful enlargement of the liver. Progression to hepatic insufficiency is relatively

common. Gastric perforation has also occurred. The MLD is 5-30 Gm. (¼-1 oz.).

Treat as for salicylate poisoning. Treat hepatic insufficiency as for carbon tetrachloride poisoning.

**Cocaine. (Local anesthetic.)**

Manifestations are restlessness, excitability, hallucinations, irregular respirations, convulsions, and circulatory failure. The MLD is 30 mg. (½ gr.).

Remove the drug from the skin or mucous membranes by washing with tap water or normal saline. Remove ingested cocaine by gastric lavage or emesis followed by catharsis. Limit absorption from an injection site by a tourniquet or ice pack. Control convulsions by giving thiopental sodium (Pentothal®). Prevent hypoxia by the administration of oxygen.

**Colechicine. (Treatment of gout)**

Manifestations are burning in the throat, watery to bloody diarrhea, cardiovascular collapse and oliguria. The MLD is 6 mg. (¼10 gr.).

Remove ingested poison by emesis or gastric lavage followed by catharsis. Give oxygen for respiratory difficulty. Treat oliguria.

**Cortisone. (Adrenal hormone.)**

Manifestations are edema, nervousness, mental depression, elevation of BP, and hirsutism (in women).

Reduce dosage slowly at the first sign of toxicity.

**Croton Oil. (Irritant)**

Manifestations are burning pain in the mouth and stomach, tenesmus, watery or bloody diarrhea, fall of BP, and coma. The MLD is 1 Gm. (15 gr.).

Remove ingested croton oil by gastric lavage or emesis followed by saline catharsis. Treat shock. Maintain hydration by giving fluids orally or I.V. Relieve pain with morphine sulfate, 10 mg. (¼6 gr.).

**Dinitrophenol. (Insecticide.)**

Manifestations are fever, prostration, thirst, excessive perspiration, difficulty in breathing, muscular tremors, and coma. Catarracts occur after repeated ingestion. The MLD is 100 mg. (1½ gr.).

Remove ingested poison by emesis, gastric lavage, and catharsis. If the body temper-

ature is elevated, reduce to normal by immersion in cold water or by applying cold packs.

#### Dioxane. (Solvent.)

Prolonged exposure may lead to kidney and liver damage and pulmonary edema.

Remove from further exposure and treat symptomatically.

#### Disulfiram (Antabuse®) Plus Alcohol. (Alcohol sensitizer.)

Manifestations are flushing, sweating, tachycardia, fall of BP, cardiac arrhythmias, air hunger, and cardiac pain.

Give artificial respiration with oxygen, and ephedrine, 25 mg. (½ gr.) subcut., or levarterenol I. V. to maintain normal BP.

#### Epinephrine, Amphetamine, & Related Drugs. (Sympathomimetics.)

Manifestations are tachycardia, dilated pupils, blurred vision, spasms, convulsions, gasping respirations, and respiratory failure. The BP is elevated initially but below normal later. The MLD is 200 mg. (3 gr.).

Remove ingested drug by emesis or gastric lavage followed by catharsis. Give artificial respiration if cyanosis is present. Maintain BP in cardiovascular collapse by the administration of fluids. Give phenolamine methanesulfonate, 5 mg. slowly I. V. Control convulsions by ether inhalation.

#### Ergot. (Uterine stimulant.)

Manifestations are rise or fall of BP, weak pulse, convulsions, and loss of consciousness. Prolonged administration causes numbness and coldness of the extremities, tingling, pain in the chest, gangrene of the fingers and toes, contractions of the facial muscles, and convulsions. The MLD is 1 Gm. (15 gr.).

Remove ingested drug by emesis or gastric lavage followed by catharsis. Treat convulsions as for strychnine poisoning.

#### Estrogens. (Female sex hormones.)

Manifestations are excessive vaginal bleeding and enlargement of the breasts. Discontinue further administration.

#### Ethylene Chlorohydrin. (Fumigant.)

Manifestations are abdominal pain, excitability, delirium, respiratory slowing, fall of

BP, twitching of muscles, cyanosis, and coma with respiratory and circulatory failure. The MLD is 5 ml.

Remove from further exposure and remove ingested poison by emesis, gastric lavage, and catharsis. Treat as for methyl bromide poisoning.

#### Ethylene Glycol. (Anti-freeze.)

The initial symptoms in massive dosage (over 100 ml. in a single dose) are those of alcoholic intoxication. These symptoms then progress to stupor, anuria, and unconsciousness with convulsions. Smaller amounts (10-30 ml.) result in anuria beginning 24-72 hours after ingestion. The urine may show calcium oxalate crystals, protein, red cells, and casts.

Remove ingested glycol by gastric lavage or emesis and catharsis. Give calcium gluconate, 10 ml. of 10% solution I. V., to precipitate oxalate. Give artificial respiration, using oxygen for depressed respiration. In the absence of renal impairment, force fluids to 4 L. or more daily to increase excretion of glycol. Treat uremia as for carbon tetrachloride poisoning.

#### Fava Beans.

Manifestations are fever, jaundice, dark urine, oliguria, and pallor. The urine may show presence of hemoglobin.

Give blood transfusions until anemia is corrected. Alkalinize urine with 5-15 Gm. (75-225 gr.) of sodium bicarbonate every 4 hours to prevent the precipitation of hemoglobin in the kidneys. In the presence of normal kidney function, maintain urine output by giving 2-4 L. of fluid daily orally or I. V. Give cortisone, 25-100 mg. daily. Treat anuria.

#### Fish Poisoning.

Manifestations are vomiting and muscular weakness progressing to paralysis, abdominal pain, and convulsions.

Remove ingested fish by gastric lavage or emesis followed by catharsis. Maintain adequate airway or give artificial respiration. Treat convulsions.

#### Fluoroacetate. (Rodenticide.)

Symptoms begin within minutes to hours with vomiting, excitability, convulsions, irregularity of the heart, and depression of respiration. The fatal dose is estimated to be 50-100 mg. (3¼-1½ gr.).

Remove ingested poison by emesis, gastric lavage, and catharsis. C.

sions as for strychnine poisoning. Monoacetin (commercial 60% glycerol monoacetate) has been suggested as an antidote. The dosage is 0.1-0.5 ml./Kg. diluted in 5 parts of saline solution I V.

#### Food Poisoning: Bacteris.

Manifestations are nausea, vomiting, diarrhea and weakness progressing for 12-24 hours. Abdominal pain may be severe. Fever, shock, and dehydration occur rarely.

Remove toxin from gastrointestinal tract by gastric lavage or emesis. If diarrhea is not present a saline cathartic may be given. Give nothing by mouth until vomiting has subsided. Then give oral fluids as tolerated for 12-24 hours before beginning a regular diet. If vomiting and diarrhea are severe, maintain fluid balance by giving 5% dextrose in saline I.V. Give codeine phosphate, 30 mg. ( $\frac{1}{2}$  gr.) orally or subcut., or camphorated tincture of opium (paregoric), 4-12 ml. (1-3 dr.) after each bowel movement. Give atropine sulfate, 1 mg ( $\frac{1}{60}$  gr.) subcut. if gastrointestinal hypersensitivity persists. Give bismuth subcarbonate, 1 Gm. (15 gr.), after each bowel movement.

#### Food Poisoning: Nitrates, Nitrites.

Manifestations are flushing of the skin, vomiting, dizziness, marked fall of BP, cyanosis, and respiratory paralysis. The MLD is 2 Gm. (30 gr.).

Remove ingested poison by gastric lavage or emesis followed by catharsis. Maintain BP by the injection of epinephrine, 1 ml. of 1:1000 solution subcut., or levarterenol. Treat methemoglobinemia by the administration of methylene blue.

#### Formaldehyde. (Disinfectant)

Manifestations are severe abdominal pain followed by cardiovascular collapse, loss of consciousness, anuria, and circulatory failure. The MLD is 60 ml. (2 oz.).

Remove ingested poison by gastric lavage or emesis followed by catharsis, preferably with 1% ammonium carbonate solution. Treat shock by administration of levarterenol and fluids.

#### Gold Salts. (Antirheumatic.)

Manifestations are skin rash, itching, eruptions, metallic taste, hepatitis, granulocytopenia, and aplastic anemia. Give dimercaprol (BAL) (see p. 779).

#### Hydralazine. (Hypotensive.)

Manifestations are fever, diffuse erythematous facial dermatitis, lymph gland enlargement, splenomegaly, arthralgia, and simulated disseminated lupus erythematosus.

Discontinue further use at the first indication of joint involvement or rash. Give acetylsalicylic acid, 1-3 Gm. (15-45 gr.) daily, or cortisone, 50-150 mg. daily, until symptoms regress.

#### Hydrogen Sulfide & Carbon Disulfide. (Fumigants.)

Manifestations are painful conjunctivitis, appearance of a halo around lights, anosmia, pulmonary edema, restlessness, blurred vision, unconsciousness, and paralysis of respiration. Prolonged exposure causes persistent low BP, impaired gait and balance, memory loss, mental depression, and parkinsonian tremor. The MAC is 20 p.p.m.

Remove from further exposure. Treat pulmonary edema.

#### Hydroquinone. (Photo developer.)

Repeated exposure will produce skin sensitivity reactions. Ingestion of 10 Gm. (150 gr.) will cause symptoms similar to those due to phenol poisoning. Treat as for phenol poisoning.

#### Ipecac, Emetine, (Emetics.)

Manifestations are fatigue, dyspnea, tachycardia, low BP, unconsciousness, and death from heart failure. The ECG reveals depressed T waves and arrhythmias. The MLD of emetine is 1 Gm. (15 gr.).

Remove ingested poison by gastric lavage or emesis followed by catharsis. Cautious digitalization may be helpful for myocardial weakness.

#### Iproniazid, Isocarboxazid, Pheniprazine,

Nialamide, Phenelzine. (Stimulants.)

Overdoses cause ataxia, stupor, excitement, fall of BP, tachycardia, and convulsions. Repeated administration may cause weakness, hallucinations, mania, urine retention, liver injury with nausea, and vomiting. The MLD is 5 Gm. (75 gr.).

Remove ingested drug by gastric lavage, emesis, and catharsis. Give artificial respiration if respiration is depressed. Maintain BP. Do not give stimulants. Discontinue administration at the first appearance of jaundice. Treat liver impairment as for carbon tetrachloride poisoning.

#### Iron Salts. (Antianemic.)

Manifestations are vomiting, diarrhea, lethargy, and low BP, progressing to circulatory collapse. The MLD is 5-10 Gm. (75-150 gr.).

Remove ingested drug by gastric lavage or emesis followed by catharsis. Give blood or

plasma transfusions to maintain BP. Give oxygen by inhalation.

#### Larkspur. (Liniment.)

Manifestations are tingling and burning sensations of the mouth and skin, vomiting, diarrhea, fall of BP, weak pulse, and convulsions.

Remove ingested poison by gastric lavage or emesis followed by saline catharsis. Give atropine, 2 mg. ( $\frac{1}{30}$  gr.) subcut. Give artificial respiration. Maintain BP.

#### Magnesium Salts. (Cathartic.)

Manifestations are watery diarrhea, gastrointestinal irritation, vomiting, tenesmus, collapse, flaccid paralysis, and, in the presence of impaired renal function, severe fall of BP. The MLD is 30-60 Gm. (1-2 oz.).

Dilute orally or rectally administered magnesium sulfate by giving tap water. Give artificial respiration if necessary. Give calcium gluconate, 10 ml. of 10% solution I.V., slowly, as a specific antidote.

#### Manganese. (Industrial.)

Ingestion causes lethargy, edema, and symptoms of extrapyramidal tract lesions. Inhalation causes bronchitis, pneumonia, and liver enlargement. Signs of parkinsonism also occur. Hepatic cell function tests may be impaired. The MAC is 6 mg./cu. mm.

Remove from further exposure. Give EDTA (see p. 784).

#### Marihuana. (Stimulant.)

Manifestations are exhilaration, hallucinations, delusions, ataxia, and coma.

Treat coma as for barbiturate poisoning.

#### Meprobamate. (Tranquilizer.)

Manifestations are drowsiness and incoordination progressing to coma with cyanosis and respiratory depression. The MLD is 12 Gm. (180 gr.).

Remove ingested drug by gastric lavage or emesis followed by catharsis. Use resuscitative measures as for barbiturates if respiratory depression is present.

#### Metal Fumes. (Industrial.)

Inhalation of zinc oxide or other metal fumes causes fever, chills, muscular aches, and weakness. Pulmonary edema may follow.

Treat pulmonary edema. Bed rest and administration of analgesics will ordinarily relieve generalized symptoms.

#### Metaldehyde. (Snail bait.)

Manifestations are severe vomiting, abdominal pains, temperature elevation, muscu-

lar rigidity, convulsions, coma, and death from respiratory failure up to 48 hours after ingestion. The MLD for adults is about 5 Gm. Treat as for acetaldehyde poisoning.

#### Methenamine. (Urinary antiseptic.)

Manifestations are skin rash, kidney and bladder irritation, hematuria, and vomiting.

Discontinue further administration.

#### Methyl Bromide & Methyl Chloride. (Fumigants.)

Manifestations are dizziness, drowsiness, fall of BP, coma, convulsions, and pulmonary edema after a latent period of 1-4 hours.

Treat convulsions as for strychnine poisoning. Treat pulmonary edema by administering 80% oxygen by face mask. Humidify inspired oxygen by using 20% ethyl alcohol in humidifier or nebulizer.

#### Methyl Sulfate. (Industrial.)

Ingestion or contact causes corrosion equivalent to that from sulfuric acid. Vapor exposure causes irritation and erythema of the eyes, pulmonary edema, proteinuria, and hematuria. The MLD for adults is about 1 Gm. (15 gr.).

Treat as for corrosive acid poisoning.

#### Metol. (Photo developer.)

Repeated exposure may cause skin sensitivity reactions characterized by weeping and crusting. Ingestion may cause methemoglobinemia with cyanosis similar to that from antipyrine.

Remove from further exposure. Treat ingestion as for antipyrine.

#### Naphthalene. (Moth balls.)

Manifestations are diarrhea, oliguria, anemia, jaundice, pain on urination, and anuria. The MLD for adults is about 2 Gm. (30 gr.).

Remove ingested naphthalene by gastric lavage or emesis followed by catharsis. Alkalinize urine by giving sodium bicarbonate, 5 Gm. (75 gr.) orally every 4 hours or as necessary to maintain alkaline urine. Give repeated small blood transfusions until hemoglobin is 60-80% of normal.

#### Naphthol. (Industrial.)

Acute poisoning is the same as that with phenol. Prolonged contact may cause bladder tumors, hemolytic anemia, and cataracts. Addition of ferric chloride to acidified urine gives a violet or blue color indicating the presence of a phenolic compound. The MLD is 2 Gm. (30 gr.).

Treat as for phenol poisoning.

**Naphthylamine. (Industrial.)**

Repeated exposure may cause skin sensitivity reactions with weeping and crusting. Exposure to large amounts may cause methemoglobinemia with cyanosis.

Remove from further exposure. Treat cyanosis as for aniline poisoning.

**Nickel Carbonyl. (Industrial.)**

Immediate symptoms are cough, dizziness, and weakness. Delayed reactions are characterized by dyspnea, cyanosis, rapid pulse, and respiratory embarrassment. The MAC is one p.p.m.

Treat cyanosis and dyspnea by giving 100% oxygen by mask. Treat pulmonary edema. Give sodium diethyldithiocarbamate, 50-100 mg./Kg. orally or I.M.

**Nicotine. (Tobacco)**

Manifestations are respiratory stimulation, nausea, diarrhea, tachycardia, elevation of BP, salivation, and, with large doses, rapid progression to prostration, convulsions, respiratory slowing, cardiac irregularity, and coma. The fatal dose of pure nicotine is about 1 mg./Kg. The MLD of tobacco is 5 Gm. (75 gr.)

Remove nicotine from skin by scrubbing or, if ingested, remove by thorough gastric lavage. Inject hexamethonium chloride, 25-50 mg. subcut. Repeat each hour until BP falls to normal. Treat convulsions as for strychnine poisoning.

**Oil of Chenopodium. (Anthelmintic.)**

Manifestations are severe gastrointestinal irritation, difficult swallowing, collapse, convulsions, and coma. The urine may show red cells and protein. The MLD is 3 Gm. (45 gr.)

Remove by gastric lavage or emesis followed by catharsis. Treat convulsions and anuria.

**Pamaquine. (Anthelmintic.)**

Hemolytic anemia and methemoglobinemia occur most commonly in Negroes. Gastric distress and weakness occur at large doses.

Reduce dosage or discontinue drug. Treat hemolytic anemia by the administration of sodium bicarbonate to alkalinize the urine and prevent the precipitation of acid hematin. Give blood transfusions if anemia is severe.

**Paraaldehyde. (Hypnotic.)**

Manifestations are deep sleep with ordinary doses and respiratory or cardiac depression occasionally with doses over 10 ml. (2½ dr.).

Treat as for acetaldehyde poisoning.

**Pentylentetrazol. (Stimulant.)**

Manifestations are increased respiration, twitching, convulsions, and respiratory failure beginning within minutes after administration. The MLD is 1 Gm. (15 gr.).

Treat as for strychnine poisoning

**Permanganate. (Antiseptic.)**

Ingestion of solid or concentrated permanganate causes laryngeal edema, necrosis of oral mucosa, slow pulse, and cardiovascular collapse. Anuria may occur. The MLD is 10 Gm. (¼ oz.).

Remove ingested poison by gastric lavage or emesis followed by catharsis. Treat shock and anuria.

**Phenolphthalein. (Laxative)**

Manifestations are erythematous, itching skin rash, or purging, collapse, and fall of BP.

Prevent further use. Treat BP fall by administration of fluids and vasoconstrictor agents.

**Phenylenediamine. (Hair dye.)**

Repeated exposures may cause sensitivity dermatitis with itching. Remove from further exposure.

**Physostigmine, Neostigmine, & Related Drugs. (Parasympathomimetics.)**

Manifestations are tremors, marked peristalsis, involuntary defecation and urination, pin-point pupils, difficult breathing, convulsions, and severe respiratory difficulty. The MLD is 6 mg. (¼ 10 gr.).

Give atropine sulfate, 2 mg. (¼ 30 gr.) I.V. or I.M. every 2-4 hours as necessary to relieve respiratory difficulty and other symptoms.

**Picrotoxin. (Stimulant.)**

Manifestations are increased respiration, twitching, convulsions, and respiratory failure, beginning 20 minutes to one hour after exposure and persisting up to 24 hours. The MLD is 20 mg. (½ 3 gr.).

Remove ingested poison by gastric lavage or emesis followed by catharsis in the absence of convulsions. Treat convulsions as for strychnine poisoning.

**Poison Hemlock.**

Manifestations are gradually increasing muscular weakness followed by paralysis with respiratory failure. Proteinuria also occurs.

Treat respiratory failure by artificial respiration with oxygen. Remove ingested poison by gastric lavage or emesis followed by catharsis.

**Poison Ivy, Poison Oak.**

Local effects begin after a delay of hours to days and include itching, swelling, vesiculation, generalized edema, proteinuria, and microscopic hematuria.

Minimize skin contamination by washing with strong soap and water. Remove ingested plant material by gastric lavage or emesis followed by saline catharsis. Treat exudative stage by exposure to air or with wet dressings of aluminum acetate, 1%. Generalized reactions may be treated with cortisone or related steroids to relieve symptoms.

**Procaine. (Local anesthetic.)**

Manifestations are dizziness, weakness, fall of BP, muscular tremors, convulsions, and cardiovascular collapse. The MLD is 1 Gm. (15 gr.).

Treat as for cocaine poisoning.

**Propylthiouracil. (Antithyroid.)**

Manifestations are skin rash, urticaria, joint pains, fever, and leukopenia.

Treat agranulocytosis by the administration of large doses of penicillin or broad-spectrum antibiotics to control intercurrent infections.

**Quinidine. (Antifibrillatory.)**

Manifestations are tinnitus, diarrhea, dizziness, falls of BP with disappearances of pulse, respiratory failure, thrombocytopenic purpura after prolonged use, urticaria, and anaphylactoid reactions. The ECG may show widening of QRS complex, lengthened Q-T interval, premature ventricular beats, and lengthened P-R interval. The MLD is 1 Gm. (15 gr.).

Remove ingested drug by gastric lavage or emesis followed by catharsis. Raise BP by I.V. saline or blood transfusions or with levarterenol. The administration of six-molar sodium lactate solution I.V. is said to reduce the cardiotoxic effects of quinidine.

**Quinine, Quinacrine, Chloroquine. (Antimalarials.)**

Manifestations are progressive tinnitus, blurring of vision, weakness, fall of BP, anuria, and cardiac irregularities. Repeated ingestion of quinine causes visual loss associated with pallor of optic disks, narrowing of retinal vessels, and papilledema. Quinacrine causes hepatitis, aplastic anemia, psychosis, and jaundice. Chloroquine causes dizziness and blurred vision. The urine may show red cells, protein, and casts. The MLD is 1 Gm (15 gr.).

Remove ingested drug by gastric lavage or emesis followed by catharsis. Treat BP

fall by cautious injection of levarterenol. Give 2-4 L. of fluids daily to promote renal excretion. Treat anuria.

**Rauwolfia. (Tranquillizer.)**

Manifestations are diarrhea, nasal stuffiness, cardiac pain, extrasystoles, congestive failure, tremors, and emotional depression.

Discontinue further administration.

**Santonin. (Anthelmintic.)**

Manifestations are yellow vision, vomiting, confusion, hallucinations, convulsions, and respiratory or circulatory failure. Urine shows hematuria, casts, and proteinuria. The MLD is 0.1 Gm. (1 1/2 gr.).

Remove ingested poison by gastric lavage or emesis followed by catharsis. Control convulsions and maintain BP.

**Shellfish**

Manifestations are numbness and tingling of lips, tongue, face and extremities, respiratory weakness or paralysis and convulsions.

Remove ingested shellfish by gastric lavage or emesis followed by catharsis. Give artificial respiration with oxygen, and maintain BP.

**Stibine. (Industrial.)**

Manifestations are weakness, jaundice, anemia, and weak pulse. The MAC is 0.1 p.p.m.

Treat as for arsenic poisoning.

**Streptomycin. (Antituberculosis.)**

Manifestations are eighth nerve injury with tinnitus, deafness, loss of sense of balance, and vertigo.

Discontinue administration at the first sign of eighth nerve injury.

**Sulfonamides. (Antibacterial.)**

Manifestations are skin eruptions, fever, hematuria, and oliguria or anuria with azotemia. The urine shows crystals, red cells, and protein.

If kidney function is normal, force fluids to 4 L. daily to speed excretion of sulfonamides. Treat anuria.

**Talc. (Dusting powder.)**

Prolonged inhalation causes fine fibrosis of the lungs and calcification of the pericardium.

Remove from further exposure. Treat as for silicosis.

**Tetrachloroethane. (Solvent.)**

Manifestations are irritation of the eyes and nose, headache, nausea, abdominal pain, jaundice, and anuria. Hepatic cell impairment

may be revealed by appropriate tests. The urine may show proteins, red cells or casts. The MLD is 1 Gm (15 gr).

Treat as for carbon tetrachloride poisoning.

#### Thallium (Rodenticide)

Thallium poisoning is characterized by slow onset of ataxia, pains and paresthesias of the extremities, bilateral ptosis, loss of hair, fever and abdominal pains. Progression of poisoning is indicated by lethargy, jumbled speech, tremors, convulsions and cyanosis, pulmonary edema and respiratory difficulty. The MLD is 1 Gm (15 gr).

Remove ingested poison by emesis, gastric lavage and catharsis. The administration of dimercaprol (see p. 779) or dithizon 20 mg/Kg/day orally for 5 days has been suggested. Maintain urine output at 1 L or more daily unless renal insufficiency appears, in which contingency only sufficient fluid to replace losses is given. Maintain BP with vasopressor agents.

#### Thalite (Insecticide)

Manifestations are respiratory difficulty and convulsions.

Remove ingested poison by emesis or gastric lavage. Treat convulsions as for strychnine poisoning.

#### Thiocyanates (Antihypertensive)

Manifestations are disorientation, weakness, low BP, psychotic behavior and convulsions. The fatal serum level of thiocyanate is 20 mg/100 ml.

Remove ingested thiocyanate by gastric lavage or emesis followed by catharsis. Give 2-4 L of fluid orally or 1 V daily to maintain adequate urine output. Remove thiocyanate by peritoneal dialysis or by hemodialysis if necessary.

#### Thioglycolates (Cold wave)

Repeated application to the skin may cause sensitivity dermatitis with edema, itching, burning and rash.

Discontinue use.

#### Thyroid

Manifestations are fever, tachycardia, hypertension and cardiovascular collapse at doses of 0.3 Gm/kg.

Maintain normal body temperature and force fluids. Digitalize if cardiac weakness is present.

#### Trichloroethylene (Solvent)

Manifestations are dizziness, headache, excitement, loss of consciousness. Irregular pulse may occur. The MLD is 5 ml.

Remove the patient to fresh air and give artificial respiration. Do not give epinephrine or other stimulants.

#### Trinitrotoluene (Explosive)

Manifestations are jaundice, dermatitis, cyanosis, pallor, loss of appetite and oliguria or anuria. The liver may be enlarged or atrophic. Hepatic cell injury may be revealed by appropriate tests. The MLD is 1 Gm (15 gr).

Remove from skin by thorough washing with soap and water. Remove swallowed trinitrotoluene by gastric lavage or emesis and catharsis. Protect liver by giving 10 ml of 10% calcium gluconate 1 V 3 times daily and a high carbohydrate and high calcium diet including at least one quart of skimmed milk daily. Give vitamin D in high doses daily.

#### Tri orthocresyl Phosphate (Plasticizer)

After 1-30 days delay, weakness of the distal muscles develops with foot drop, wrist drop and loss of plantar reflex. Death may occur from respiratory muscle paralysis. The MLD for adults is about 5 Gm (75 gr).

Remove by gastric lavage or emesis followed by catharsis. Maintain respiration if necessary by tank respirator.

#### Vanadium (Industrial)

Manifestations are rhinorrhea, sneezing, sore chest, dyspnea, bronchitis and pneumonitis.

Give ascorbic acid 1 Gm (15 gr)/day.

#### Veratrum, Zygadenus (Hypotensives)

Manifestations are nausea, severe vomiting, muscular weakness, slow pulse and low BP. Excessive amounts may cause marked rise in BP.

Remove ingested poison by gastric lavage or emesis followed by catharsis. Atropine 2 mg (1/30 gr) subcut will block the reflex fall of BP and the bradycardia. Elevation of BP is treated by the administration of phenolamine hydrochloride 25 mg subcut repeated every 4 hours.

#### Volatile Anesthetics: Ether, Chloroform

Halothane, Diethyl Ether, Cyclopropane, Ethyl Chloride, Ethylene Nitrous Oxide.

Manifestations are excitement, unconsciousness, depression and paralysis of respiration. Cardiac irregularities occur with cyclopropane, chloroform and halothane. Severe fall of BP or cardiac arrest may also occur. The MLD is 1-30 ml.



Remove volatile anesthetic by artificial respiration. Maintain BP by I V, saline, blood transfusions, and levarterenol. Prevent hypoxia by administering oxygen.

**Volatile Oils.** (Turpentine, pine oil, menthol, absinthe, savin, pennyroyal, eucalyptus )

Manifestations are vomiting, diarrhea, unconsciousness, shallow respiration, hematuria, and convulsions. The MLD is 15 Gm. (1/2 oz.).

Give 60-120 ml. (2-4 oz.) of liquid petrolatum or castor oil and then remove oils by gastric lavage, taking care to prevent aspiration. Follow with a saline cathartic. Give artificial respiration if necessary. Give fluids, 2-4 L., daily if kidney function is normal after the danger of pulmonary edema has passed.

#### **Water Hemlock.**

Manifestations are abdominal pain, vomiting, diarrhea, convulsions, cyanosis, and respiratory failure.

Treat as for hemlock poisoning

#### **Zinc Stearate.** (Dusting powder.)

Inhalation causes fever, dyspnea, cyanosis, and bronchial pneumonia.

Give penicillin, one million units I M daily, or a broad-spectrum antibiotic to prevent bronchial pneumonia.

#### **Zinc Sulfate.** (Astringent.)

Manifestations are burning pain in the mouth and throat, vomiting, diarrhea, anuria, and cardiovascular collapse. The MLD is 30 Gm (1 oz.).

Give milk or starch drinks to dilute the poison and remove by gastric lavage. Replace fluid loss with 5% dextrose in saline. Relieve pain by giving morphine sulfate, 10 mg, (1/6 gr.)

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#### **Bibliography.**

See p. 770.

# ***Appendix:***

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## UNESTABLISHED DRUGS

In this book a conservative approach is favored whenever a choice has to be made among various drugs available for the treatment of a given disorder. In some cases it is not possible or necessary to make a choice, e g., where equally good alternatives are available or where there are differences of opinion among physicians about the relative efficacy of alternative regimens, and in these instances all of the appropriate medications and dosage schedules are given in the text.

In some cases, however, there are clear justifications for omitting preparations which have been proposed for use in clinical practice. With the exceptions noted in the discussions below, the following principles have been adhered to in the drug sections of this book: (1) Proprietary combinations of drugs are, in general, omitted. (2) "Repeat-dosage" and "prolonged-dosage" preparations are not listed. (3) Standard, well-established and familiar drugs are, in general, preferred. (4) Drugs whose usefulness has not been established by the conventional and approved pharmacologic and clinical techniques are not recommended.

### Proprietary Combinations.

Unless there is a clear pharmacologic indication, combinations of drugs in fixed proportions are not listed. There are of course many exceptions, e g., in skin diseases where stubborn dermatoses can often be treated effectively only by means of multiple-ingredient mixtures worked out on a more or less empiric basis, or in the case of ephedrine and phenobarbital, where the barbiturate is used to reduce the unpleasant CNS effects of the ephedrine. In some cases also, drug combinations are a convenience to the patient, e g., when treating senile patients with many different remedies.

As a rule, however, drugs should be given in individualized doses, if two drugs are needed separate administration has the advantage of flexibility, making it possible to increase the dose of one without increasing the dose of the other. Furthermore, in many of the drug combinations available one or more of the ingredients are present in amounts so small as to have little therapeutic value (although they may exert a sensitizing effect). Many drug combinations are simply irrational and a few are dangerous.

Combination preparations have the additional disadvantage of being usually more expensive than the same drugs prescribed individually.

### Repeat-dosage & Prolonged-dosage Preparations.

Special dosage forms designed to deliver repeated or continuous quantities of orally administered drugs by varying the solubilities of their coatings have not been recommended. The best objective evidence at present is that their onset and duration of effect are unpredictable. Most appear to release the total dose at once.

### Standard Drugs Preferred.

Wherever possible we have recommended those drugs which are considered "standard" or established. These are the drugs which have been used widely or for a long time. The advantage they offer is that their toxicities are known, their properties are discussed in the appropriate reference works, and their dosage schedules have usually been determined on the basis of long experience. From time to time a new drug or a new form of an old drug will be offered to replace a standard drug. However, unless an unmistakably clear indication for abandoning a familiar remedy in favor of a new one can be presented, it is advisable to continue to use the established preparations.

### Drugs of Questionable Usefulness.

Many drugs even though widely used, have not been shown to be of value in the treatment of the disorders for which they are intended. Some preparations in this category have achieved such currency that explanatory and precautionary comments about them are incorporated into the text. In the following pages are listed a few drug groups, with examples and recommended doses, whose usefulness has not been demonstrated by adequate clinical trials. Some of these drugs may eventually prove their worth, but as of this writing they should be regarded as ineffective preparations which should not be used except for their placebo effect.

## UNESTABLISHED USES OF VASODILATORS

The beneficial effects of giving vasodilators intra-arterially soon after acute arterial occlusion are discussed on p. 244. The use

of these agents in the management of chronic vascular insufficiency has also been suggested. However, properly conducted clinical trials have failed to show that chronic administration of these drugs is of any value in the treatment for example of atherosclerotic occlusion. The poor results achieved may be due to the fact that vessels in ischemic areas are already dilated to the limit of their ability even before any drug is administered. Generalized vasodilatation lowers perfusion pressure but does not redistribute blood flow and increased flow in crucial areas is not achieved.

There is some evidence that these drugs may actually be harmful in the treatment of atherosclerosis. As noted on p. 243, blood flow studies show that the blood flow in ischemic limbs of elderly people with arteriosclerosis is decreased not increased by vasodilator drugs administered systemically.

Vasodilators which have not proved useful are listed in the table below.

### VOLUNTARY MUSCLE RELAXANTS

The drugs listed below have been suggested for the relief of voluntary muscle spasm or tension associated with joint or muscle disease. It is postulated that they exert

their effect by depressing multisynaptic pathways in the spinal cord. The muscle relaxants do depress the spinal cord in the laboratory and transiently when administered I.V. to humans. However, adequate clinical trials have not shown that oral administration has any specific muscle relaxant effect.

All of the sedative-hypnotic drugs are effective depressants of intermuscular transmission and sedation itself often relieves muscle tension. It is not surprising therefore that many of the muscle relaxants have the same primary and side effects as the sedatives.

The drugs in this class are as follows (The dosages given are those suggested by the manufacturers to be administered orally 3 or 4 times daily.)

Carisoprodol (Soma® Relaxin®)	250 350 mg
Chlormezanone (Trancopal®)	100 200 mg
Chlorzoxazone (Paraflex®)	250 500 mg
Mephenesin (Tolserol® many brand names)	2 3 Gm
Mephenesin carbamate (Tolseram®)	2 3 Gm
Methocarbamol (Robaxin®)	1 5 2 Gm
Phenylramidol (Analgin®)	200 400 mg
Styrzmate (Sinaxer®)	400 mg

### Vasodilating Agents

Drug	Recommended Doses	Remarks
Phenoxybenzamine (Dibenzylamine®)	10 30 mg b i d orally p c	Blockade of vasoconstrictor (sympathetic) fibers achieved after oral administration. Generalized vasodilation, postural hypotension, nausea prominent. Long delay before effect. Increase dose slowly.
Tolazoline (Priscoline®)	12 5 50 mg 3 4 times daily p c	Classed as sympatholytics but also have direct histamine-like and acetylcholine-like effects on vessels. Increase heart rate and output.
Azaperone (Mildar®)	25 50 mg 3 4 times daily p c	
Papaverine	30 60 mg 1 V every 3 4 hours	
Cyclandelate (Cyclospasmol®)	100 300 mg q i d orally	Generalized direct effect of relaxing smooth muscle.
Nicotinic acid niacin	See p. 513	
Beta-pyridyl carbinol (nicotinyl alcohol Rontacol®)	50 150 mg t i d orally p c	Cutaneous vasodilators primarily in bluish area.
Nylidrin (Arlidin®)	6 mg 3 6 times daily orally	Sympathomimetics comparable to isoproterenol.
Isosuprine (Vasodilan®)	10 20 mg 3 4 times daily orally	Generalized smooth muscle relaxation plus cardiac stimulation.

## ANALEPTICS

The convulsant central stimulant drugs or analeptics should no longer be considered useful in the management of drug toxicity or in resuscitation. The same objections apply to all of the drugs in this group: the danger of producing convulsions, fever, and cardiac arrhythmias.

The drugs in this group are listed here for purposes of identification only:

- Bemegride (Megimide®)
- Caffeine and sodium benzoate
- Ethamivan (Emivan®)
- Nikethamide (Coramine®)
- Pentylentetrazol (Metrazol®)
- Picrotoxin

## UNESTABLISHED VITAMINS

The vitamins which are important in human nutrition are discussed on pp. 588-91. In general, most clinicians feel that "routine" vitamin supplementation for people who do not have deficiency diseases is wasteful and unnecessary, and there are many instances in which actual toxicity has resulted from enthusiastic self-medication with these substances.

There are no indications for the use of any of the following vitamins:

### Vitamin E

Vitamin E (tocopherols, wheat germ oil) has never been shown to play a role in human nutrition, and the claims for its usefulness in cardiovascular disease and other diseases in humans have not been substantiated. It nevertheless continues to be available, both by itself and in various combinations with other vitamins.

### Vitamin P

Mixed flavonoids from citrus fruits, rutin, and hesperidin are available, usually in combination with vitamin C or vitamin K, but there is no reason to believe that they have any effect on vascular disorders. The flavonoids periodically attract lay interest as cold cures.

### Lipotropic Agents.

Choline is still suggested as a lipotropic agent in the treatment of fatty infiltration of

the liver. Choline is present in adequate amounts in the average diet, and in addition can be synthesized in the body. An effect on cirrhosis or atherosclerosis has not been demonstrated in adequate clinical trials.

### Dexpanthenol.

Dexpanthenol (pantothenyl alcohol, Cozyme®, Ilopan®) in its active form is a constituent of an enzyme which is important in acetylation reactions. It has been suggested that it can be used to increase the action of acetylcholine on the intestine and in this way correct paralytic ileus. Its ineffectiveness has been repeatedly established.

## ENZYMES

The possible usefulness of several enzymes in treatment is discussed above. In addition, there are 2 groups of enzymes of doubtful utility but wide use.

### Anti-inflammatory Enzymes.

The claim is made that several enzymes are capable of hastening the resolution of acute inflammatory states, especially those due to trauma or those associated with extravasation of blood. These drugs are available in oral, transbuccal, and injectable forms. Included are proteolytic enzymes of animal origin such as trypsin (Parezyme®, Tryptar®), chymotrypsin (Avazym®, Chymar®), or mixtures of the two (Chymoral®, Orenzyme®), vegetable proteases (Papase®, Ananase®), bacterial streptokinase-streptodornase (Vari-dase®) and one alpha-amylase (Fortizyme®, Buclamase®). The claims of usefulness for these drugs are not supported by controlled trials, and the injectable enzymes, notably chymotrypsin, have been responsible for anaphylactic reactions.

### Fibrinolytic Enzymes.

Fibrinolysin or plasmin is an enzyme capable of dissolving fibrin clots. Streptokinase is an enzyme which upon application leads to activation of fibrinolysin within the body. A mixture of the 2 components, marketed as human fibrinolysin (Actase®, Thrombolylin®), is available. In the dosages and by the routes practicable in humans, this preparation does not have any demonstrable effects in spite of its theoretical and potential interest.

# SOME RECENTLY INTRODUCED & INVESTIGATIONAL DRUGS (INCLUDING DRUGS RECENTLY WITHDRAWN)

**Acetohexamide (Dymecor®)** Investigational  
An oral antidiabetic agent now undergoing  
clinical trial

**Acetophenazine (Tindal®)** A phenothiazine  
type tranquilizer

**Alpha aminobenzyl penicillin (Penbritin®  
P 50)** Investigational A semi synthetic  
penicillin of special interest because of its  
greater activity against gram negative  
bacteria

**Amphenidone (Dornwal®)** A sedative with  
drawn from the market

**Amtriptyline (Elavil®)** 1961 An antidepressant  
See p 504

**Angiotensin amide (Hypertensin®)** 1962 A  
potent polypeptide pressor agent still in  
completely studied as an alternative to  
levarterenol

**Betamethasone (Celestons®)** 1961 An anti  
inflammatory steroid See p 578

**Bromindione (Halinone®)** Investigational An  
indandione anticoagulant

**Chlorprothixene (Taractan®)** 1962 A tran-  
quilizer See chart on p 503

**Colistimethate (Coly Mycin®)** 1961 See  
p 667

**Cyproheptadine (Periactin®)** 1961 An anti-  
histamine which like several other anti-  
histamines can also antagonize serotonin  
in the laboratory

**Diazepam (Valium®)** Investigational Virtu-  
ally a duplicate of chlordiazepoxide (see p  
501)

**Dimethylpyridine (Forhlistal®)** 1961 See  
Antihistamines p 8

**Dipyridamol (Persantin®)** 1961 A vaso-  
dilator suggested for use in the prevention  
of anginal attacks Acceptable evidence of  
its usefulness has not yet been provided

**Dromostanolone (Drolban®)** 1961 An andro-  
genic steroid suggested for use in carci-  
noma of the breast

**Dydrogesterone (Duphaston®)** 1962 Also  
called isopregnenone A progestational  
steroid See p 582

**Edetate calcium disodium (Calcium Disodium  
Versenate®) and edetate, disodium (Endrate  
Disodium®)** 1962 These generic names  
replace the earlier edathamil

**Ethamivan (Emivan®)** 1961 A CNS stimu-  
lant See p 805

**Etryptamine (Monase®)** An MAO inhibitor  
used briefly as a central stimulant With-  
drawn from the market

**Fluocinolone (Synalar®)** 1961 An anti-  
inflammatory steroid for topical use

**5 Fluorouracil (Fluorouracil®)** 1962 An  
agent being used cautiously and tentatively  
on selected patients with solid tumors

**Fluprednisolone (Alphadrol®)** 1961 An  
anti inflammatory steroid See p 578

**Flurandrenolone (Cordran®)** 1961 A topical  
anti inflammatory steroid

**Hydroxyphenamate (Listica®)** 1961 A  
sedative hypnotic comparable to mepro-  
bamate

**IDU, SKF 14287** Investigational A uridine  
analogue reportedly effective in herpes  
keratitis See p 100

**Iproniazid (Maralid®)** An amine oxidase  
inhibitor type of CNS stimulant withdrawn  
from the market

**Levopropoxyphene (Novrad®)** 1962 An  
isomer of Darvon® used as a nonnarcotic  
cough suppressant comparable to dextro-  
methorphan

**Mebutamate (Capla®)** 1961 A meprobamate  
analogue advertised without acceptable  
basis for the treatment of hypertension

**Methopyrapone (Metopirone®)** 1962 This  
drug inhibits 11 hydroxylation i.e. syn-  
thesis of aldosterone and cortisol If ex-  
cretion of 17 hydroxy steroids is measured  
after its administration assay of pituitary  
function results

**Methotrimeprazine (Levomepromazine, Nozi-  
nan®)** Investigational A phenothiazine  
tranquillizer which after injection (but not  
after oral administration) also has anal-  
gesic effects

**Methoxyflurane (Penthrane®)** 1962 A gen-  
eral anesthetic comparable to halothane  
Fluothane®

**Methoxypromazine (Tentone®)** A phenothi-  
azine tranquilizer withdrawn from the  
market

- Methyldopa (Aldomet®)** Investigational A mild hypotensive drug now being widely tested It does not act by the mechanism originally hypothesized
- Methysergide (Sansert®)** 1962 An ergot derivative used in the treatment of migraine
- Metronidazole (Flagyl®)** Investigational This drug is of undoubted usefulness in the treatment of *Trichomonas* infections Its release has been delayed for unspecified reasons Reported adverse effects include allergic reactions, candidal overgrowth and adrenal cortex inhibition
- Norinyl®** Investigational A progestin-estrogen mixture used as an oral contraceptive See p 582
- Ortho-Novum®** Investigational A progestin-estrogen mixture used as an oral contraceptive See p 582
- Oxacillin sodium (Prostaphyllin®, Resistopen®)** 1962 A semi-synthetic, oral penicillin not destroyed by penicillinase and therefore, very useful in the treatment of other wise resistant staphylococcal infections See p 657
- Oxyphenbutazone (Tandearil®)** 1961 A phenylbutazone analogue See p 418
- Paramethasone (Haldron®)** 1961 An anti-inflammatory steroid See p 578
- Pargyline (Eutonyl®)** Investigational An MAO inhibitor that is not a hydrazide Currently being evaluated for treatment of hypertension
- Paromomycin (Humatin®)** 1962 An antibiotic not absorbed from the gastrointestinal tract Suggested for use in amebiasis
- Phendimetrazine (Plegine®)** 1961 An anorexiant comparable to amphetamine See p 592
- Pheniprazine (Catron®)** An amine oxidase inhibitor type of CNS stimulant withdrawn from the market
- Poldine methylsulfate (Nacton®)** 1961 See atropine substitutes p 323
- Polythiazide (Renese®)** 1961 A thiazide diuretic See p 237
- Propiomazine (Largan®)** 1961 A phenothiazine tranquilizer Available only in injectable form
- Stanozolol (Winstrol®)** 1962 See Anabolic hormones, p 581
- Sulfachlorpyridazine (Sontlyn®)** 1962 A sulfonamide excreted over a period intermediate between the "long-acting" and ordinary sulfonamides No advantage is apparent
- Sulfamethoxazole (Gantanol®)** 1961 A sulfonamide exactly comparable to sulfisoxazole although possibly more allergenic
- Thalidomide (Kevadon®)** A somnifacient now notorious for its ability to cause phocomelia Not marketed in the U S A but available under controls elsewhere
- Thiethylperazine (Torecan®)** 1961 A phenothiazine suggested for use as an antiemetic See p 303
- Tranlycypromine (Parnate®)** 1961 See p 505
- Triparanol (MER/29®)** An inhibitor of cholesterol synthesis briefly investigated for use in atherosclerosis Withdrawn because of occurrence of cataracts, skin changes, and baldness
- Zoxazolamine (Flexin®)** A voluntary muscle relaxant (see p 804) withdrawn from the market

## GLOSSARY OF GENETIC TERMS

- Abiotrophic disease** Genetically determined disease which is not evident at birth but which becomes manifest later in life
- Acquired;** Not hereditary, contracted after birth or in utero (cp Hereditary)
- Alleles** See Allelic genes
- Allelic genes** Paired genes or partner genes, genes occupying the same locus on homologous (paired) chromosomes and which, therefore, normally segregate from each other during the reduction division of mitosis
- Allelomorphic genes** See Allelic genes
- Analogous** Similar in structure but not of the same origin
- Autosomes** The chromosomes (22 pairs of autosomes in man) other than the sex chromosomes (cp Sex chromosome)
- Chromosome** A small thread-like or rod like structure into which the nuclear chromatin divides during mitosis. The number of chromosomes is constant for any given species (23 pairs in man, 22 pairs of autosomes and one pair of sex chromosomes). Each chromosome is composed of a linear arrangement of small bodies called genes, each of which occupies a specific locus on its chromosome
- Congenital** Existing at or before birth, not necessarily hereditary (cp Familial)
- Diploid** Pertaining to the number of chromosomes of the zygote, which is twice the number in each gamete (cp Haploid)
- Dominant** Designating a gene whose phenotypic effect largely or entirely obscures that of its allele (cp Recessive)
- Eugenics** The science dealing with factors which improve the hereditary qualities of future generations, especially the human race
- Familial** Pertaining to traits, either hereditary or acquired, which tend to occur in families
- Gamete (germ cell)** A cell which is capable of uniting with another cell in sexual reproduction (i.e., the ovum and spermatozoon)
- Gene** A unit of heredity which occupies a specific locus in the chromosome which, either alone or in combination produces a single characteristic. It is usually a single molecule which is capable of self-duplication or mutation
- Genetic carrier state** A condition wherein a given hereditary characteristic is not manifest in one individual but may be genetically transmitted to the offspring of that individual
- Genetics** The science concerned with the phenomena of inheritance and biologic variation
- Genotype** The hereditary constitution, or combination of genes, which characterizes a given individual or a group of genetically identical organisms (cp Phenotype)
- Germ cells (gametes)** Cells capable of uniting with other cells sexually in reproducing the organism (cp Somatic cells)
- Haploid** Pertaining to the number of chromosomes in each gamete, i.e., a single set of chromosomes (cp Diploid)
- Hereditary.** Transmitted from ancestor to offspring through the germ plasma (cp Acquired)
- Heterozygotic (Disygotic or Fraternal) Twins** Twins derived from 2 distinct fertilized ova (cp Homozygotic Twins)
- Heterozygous;** Having 2 members of a given hereditary factor pair which are dissimilar, i.e., the 2 genes of an allelic pair are not the same (cp Homozygous)
- Homologous chromosomes;** Paired or sister chromosomes resulting from normal mitosis
- Homozygotic (Monozygotic or Identical) Twins** Twins derived by division of one fertilized ovum into 2 at an early stage of development (cp Heterozygotic Twins)
- Locus** The specific site of a gene in a chromosome
- Meiosis** A special type of cell division occurring during the maturation of sex cells, by which the normal diploid set of chromosomes is reduced to a single (haploid) set, 2 successive nuclear divisions occurring while the chromosomes divide only once
- Mutation** A transformation of a gene, often sudden and dramatic, with or without known cause, into a different gene occupying the same locus as the original gene on a particular chromosome, the new gene is allelic to the normal gene from which it has arisen



**Nondisjunction** Failure of a sister pair of chromosomes to separate properly at cell division

**Pedigree** A table or diagram illustrating ancestral lineage a genealogy

**Penetrance** The likelihood or probability that a gene will become morphologically (phenotypically) expressed The degree of penetrance may depend upon acquired as well as genetic factors

**Phenotype** The visible characteristics of an individual or those which are common to a group of apparently identical individuals (cp Genotype)

**Proband** *An individual demonstrating a given hereditary trait or characteristic who is detected independently of the other members of the family The first proband detected is referred to as the index case or propositus*

**Recessive** Designating a gene whose phenotypic effect is largely or entirely obscured by the effect of its allele (cp Dominant)

**Reduction division** A division involving the separation of members of a homologous pair of chromosomes a reduction to the haploid state

**Segregation** The separation of 2 genes of a pair in the process of maturation so that only one goes to each germ cell

**Sex chromosome** The chromosome or pair of chromosomes which determines the sex of the individual (cp Autosomes) (In the human female the sex chromosome pair is homologous XX in the male nonhomologous XY)

**Sex linkage** The influence of sex on transmission of hereditary traits There are 2 main types of sex linked inheritance depending upon whether the sex linked genes are located in the X or the Y chromosome Sex linkage may be absolute or incomplete

**Sibship** Children of the same parents (Also sometimes used to signify all blood relations)

**Somatic cells** *Cells incapable of reproducing the organism (cp Germ cells)*

**Translocation** The attachment of extra chromosomal material to another chromosome probably resulting from an unequal exchange of chromosomal substance between 2 different chromosomes during cell division

**Trisomy** The existence of 3 chromosomes of one variety rather than the normal pair of chromosomes

**Zygote** The cell formed by the union of 2 gametes in sexual reproduction

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## CHEMICAL ANALYSIS OF BLOOD & BODY FLUIDS\*

**Albumin, Serum.** See Protein, serum.

**Ammonia, Blood.** [Normal (Conway) 40-70 mcg./100 ml. whole blood.]

**A Precautions** Do not use anticoagulants containing ammonia, e.g., ammonium oxalate or edathamil (EDTA). The determination should be done immediately after drawing blood. If the blood is kept in an ice-water bath it may be held for up to one hour.

**B Physiologic Basis** Ammonia present in the blood is derived from 2 principal sources (1) in the large intestine putrefactive action of bacteria on nitrogenous materials releases significant quantities of ammonia. (2) In the process of protein metabolism, ammonia is liberated. Ammonia entering the portal vein or the systemic circulation is rapidly converted to urea in the liver. Liver insufficiency may result in an increase in blood ammonia concentration especially if protein consumption is high or if there is bleeding into the bowel.

**C Interpretation** Blood ammonia is elevated in hepatic insufficiency or with liver by-pass in the form of a portacaval shunt particularly if protein intake is high or if there is bleeding into the bowel.

**D Method** Strong alkali is added to the blood to liberate ammonia, which is then trapped in acid. The quantity of ammonia collected is then determined by titration or by nesslerization.

**Amylase, Serum.** (Normal 80-180 Somogyi units/100 ml. serum.) (One unit equals amount of enzyme which will produce 1 mg. of reducing sugar from starch at pH 7.2.)

**A. Precautions** If storage for more than one hour is necessary, blood or serum must be refrigerated.

**B. Physiologic Basis** Normally, small amounts of amylase (diastase) originating in the pancreas and salivary glands are present in the blood. Inflammatory disease of these glands or obstruction of their ducts results in regurgitation of large amounts of enzyme into the blood.

### C. Interpretation

1. Elevated In acute pancreatitis, obstruction of pancreatic ducts (carcinoma, stone, stricture, duct sphincter spasm after morphine), mumps, occasionally in the presence of renal insufficiency, occasionally in diabetic acidosis, and occasionally with inflammation of the pancreas from a perforating peptic ulcer.

2. Decreased in hepatitis, acute and chronic, pancreatic insufficiency, and occasionally in toxemia of pregnancy.

**D Method** Serum is incubated with buffered starch solution and the amount of reducing sugar produced is determined.

**Amylase, Urine.** (Normal Varies with method.)

**A Precautions** If the determination is delayed more than one hour after collecting the specimen, urine must be refrigerated.

**B. Physiologic Basis** See Amylase, Serum. If renal function is adequate, amylase is rapidly excreted in the urine.

**C Interpretation** Elevation of the concentration of amylase in the urine occurs in the same situations in which serum amylase concentration is elevated. Urinary amylase concentration remains elevated for up to 7 days after serum amylase levels have returned to normal following an attack of pancreatitis. Thus the determination of urinary amylase may be useful if the patient is seen late in the course of an attack of pancreatitis.

**D Method** Urine is incubated with buffered starch solution. The amount of unhydrolyzed starch remaining may be determined using iodine as an indicator, or the amount of reducing sugar may be determined. The result is reported in terms pertinent to the method employed.

**Bicarbonate, Serum or Plasma** (measured as  $\text{CO}_2$  content). (Normal 24-28 mEq./L. or 55-65 Vol.%. )

**A Precautions** Plasma or serum is preferably drawn under oil and handled anaerobically.

**B. Physiologic Basis** Bicarbonate-carbonic acid buffer is one of the most important buffer systems in maintaining normal pH of body fluids. Bicarbonate and pH determinations on plasma serve as a basis for assessing "acid-base balance."

### C Interpretation

1. Elevated in -

(1) Metabolic alkalosis (arterial blood pH increased) due to ingestion of large quantities

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of sodium bicarbonate, protracted vomiting of acid gastric juice, accompanying potassium deficit.

(2) Respiratory acidosis (arterial blood pH decreased) due to pulmonary emphysema or hypoventilation due to oversedation, narcotics, or inadequate artificial respiration.

## 2. Reduced in -

(1) Metabolic acidosis (arterial blood pH decreased) due to diabetic ketosis, starvation, persistent diarrhea, renal insufficiency, ingestion of excess acidifying salts, or salicylate intoxication.

(2) Respiratory alkalosis (arterial blood pH increased) due to hyperventilation

**D Method** The serum or plasma is acidified and the liberated  $\text{CO}_2$  measured in a special volumetric or manometric apparatus.

**Bilirubin, Serum.** [Normal Direct (glucuronide), 0.1-0.4 mg./100 ml. Indirect (unconjugated) 0.2-0.7 mg./100 ml.]

**A. Precautions** The fasting state is preferred to avoid turbidity of serum.

**B. Physiologic Basis** Destruction of hemoglobin yields bilirubin, which is conjugated in the liver to the diglucuronide and excreted in the bile. Bilirubin accumulates in the plasma when liver insufficiency exists biliary obstruction is present, or the rate of hemolysis increases. Rarely abnormalities of enzyme systems involved in bilirubin metabolism in the liver (e. g., absence of glucuronyl transferase) result in abnormal bilirubin concentrations.

## C. Interpretation

1. Direct and indirect forms of serum bilirubin are elevated in acute or chronic hepatitis and biliary tract obstruction (cholelithiasis, hepatic, or common ducts)

2. Indirect serum bilirubin is elevated in hepatitis due to toxic agents such as drugs,  $\text{CCl}_4$ , hemolytic diseases or reactions, and Gilbert's disease (absence or deficiency of glucuronyl transferase).

**D Method** Serum or plasma may be used. Bilirubin is determined colorimetrically by coupling with a diazo reagent. Direct bilirubin is determined in aqueous solution, indirect bilirubin after addition of methyl alcohol.

**Calcium, Serum.** (Normal 9-11 mg./100 ml. or 4.5-5.5 mEq./L.)

**A. Precautions** Glassware must be free of calcium. The patient should be fasting. Serum should be promptly separated from the clot.

**B Physiologic Basis** Endocrine, renal gastrointestinal, and nutritional factors normally provide for precise regulation of calcium concentration in plasma and other body fluids. Since some calcium is bound to plasma protein, especially albumin, determination of the plasma albumin concentration is necessary before the clinical significance of abnormal serum calcium levels can be interpreted accurately

## C Interpretation

1. Elevated in hyperparathyroidism, vitamin D excess osteolytic disease, such as multiple myeloma, invasion of bone by metastatic cancer, and Boeck's sarcoid

2. Decreased in hypoparathyroidism, vitamin D deficiency (rickets, osteomalacia) renal insufficiency, hypoproteinemia, malabsorption syndrome (sprue, ileitis, celiac disease, pancreatic insufficiency), and severe pancreatitis with pancreatic necrosis.

**D Method** Calcium is precipitated as oxalate or phosphate. Oxalate is measured by titration with  $\text{KMnO}_4$ . Phosphate is measured by colorimetric reaction. Calcium equivalent is then calculated. Determination by flame photometry or by titration with chelating agents is not yet employed routinely in most clinical laboratories

**Calcium, Urine, Daily Excretion.**

Ordinarily there is a moderate continuous urinary calcium excretion of 50-150 mg./100 ml., depending upon the intake.

**A Procedure** The patient should remain upon a diet free of milk or cheese for 3 days prior to testing, for quantitative testing a neutral ash diet containing about 150 mg. calcium per day is given for 3 days. Quantitative calcium excretion studies may be made on a carefully timed 24-hour urine specimen. The screening procedure with the Sulkowitch reagent is simple and useful.

**B Interpretation** On the quantitative diet a normal person secretes  $125 \pm 50$  mg. of calcium per 24 hours. Normally, a slight (1+) cloud reaction (Sulkowitch) occurs if milk and cheese are not present in the diet. In hyperparathyroidism, the urinary calcium excretion usually exceeds 200 mg./24 hours.

**Carbon Dioxide Combining Power, Serum or Plasma.** (Normal 24-29 mEq./L. or 55-75 Vol./100 ml.)

Plasma or serum  $\text{CO}_2$  combining power is elevated or decreased in the same clinical circumstances as plasma or serum bicarbonate. Anaerobic handling of the specimen is

not necessary. The method is the same as for bicarbonate determination except that the serum or plasma is exposed to an "alveolar" air concentration of  $\text{CO}_2$  (i.e., 40-50 mm. Hg partial pressure or 5-6%  $\text{CO}_2$ ) prior to the determination.

See Bicarbonate, above, for interpretation.

**Chloride, Serum or Plasma.** (Normal 100-106 mEq./L. or 350-375 mg./100 ml.)

**A. Precautions** Determination on whole blood yields lower results than those obtained using serum or plasma as the specimen. Always use serum or plasma.

**B. Physiologic Basis** Chloride is the principal inorganic anion of the extracellular fluid. It is important in maintenance of acid-base balance even though it exerts no buffer action. When chloride as  $\text{HCl}$  or  $\text{NH}_4\text{Cl}$  is lost, alkalosis follows when chloride is retained or ingested acidosis follows. Chloride (with sodium) plays an important role in control of osmolarity of body fluids.

#### C. Interpretation

1. Elevated in renal insufficiency (when  $\text{Cl}$  intake exceeds excretion) nephrosis (occasionally) renal tubular acidosis, uretero-sigmoid anastomosis (reabsorption from urine in gut) dehydration (water deficit) and overtreatment with saline solution

2. Decreased in gastrointestinal disease with loss of gastric and intestinal fluids (vomiting of acid gastric juice, diarrhea gastrointestinal suction) renal insufficiency (with salt deprivation) overtreatment with diuretics chronic respiratory acidosis (emphysema), diabetic acidosis, excessive sweating adrenal insufficiency ( $\text{NaCl}$  loss) hyperadrenocorticism (chronic  $\text{K}^+$  loss), and metabolic alkalosis ( $\text{NaHCO}_3$  ingestion,  $\text{K}^+$  deficit).

**D. Method** Chloride is precipitated by titration with  $\text{Ag}^+$  salts or  $\text{Hg}^{++}$  salts. The end-point is determined colorimetrically or potentiometrically.

#### Chloride, Urine.

Urine chloride content varies with dietary intake, acid-base balance, endocrine "balance," body stores of other electrolytes, and water balance. Relationships and responses are so variable and complex that there is little clinical value in urine chloride determinations other than in balance studies

**Cholesterol, Plasma or Serum.** (Normal, 150-280 mg./100 ml.)

**A. Precautions** The fasting state is preferred.

**B. Physiologic Basis** Cholesterol concentrations are determined by metabolic functions which are influenced by heredity, nutrition, endocrine function, and integrity of vital organs such as the liver and kidney. Cholesterol metabolism is intimately associated with lipid metabolism.

#### C. Interpretation

1. Elevated in familial hypercholesterolemia (xanthomatosis), hypothyroidism, poorly controlled diabetes mellitus, nephrotic syndrome, chronic hepatitis, biliary cirrhosis, obstructive jaundice, hypoproteinemia (idiopathic, with nephrosis or chronic hepatitis), and lipemia (idiopathic, familial).

2. Decreased in acute hepatitis and Gaucher's disease, occasionally in hyperthyroidism, acute infections, anemia, malnutrition

**D. Method** Cholesterol is extracted from plasma or serum with alcohol-ether mixture. After evaporation of the solvent, the residual cholesterol is measured by the Liebermann-Burchard reaction, a color reaction employing sulfuric acid and acetic anhydride. Other colorimetric procedures employ ferric ion.

#### Cholesterol Esters, Plasma or Serum.

(Normal 65-75% of total serum or plasma cholesterol.)

**A. Precautions** None.

**B. Physiologic Basis** Cholesterol is esterified in the intestinal mucosa and in the liver. Cholesterol exists in plasma or serum as the free form (25-33% of total) and as the ester (67-75% of total). In the presence of acute hepatic insufficiency (as in acute hepatitis), the concentration of esters is reduced.

#### C. Interpretation

1. Elevated along with cholesterol in absence of hyperbilirubinemia (see Cholesterol, above). The ratio of ester/total cholesterol under these circumstances is normal. With hyperbilirubinemia absolute values may be elevated but not in the same proportion as total cholesterol, so that the ester/total cholesterol ratio is less than 65%.

2. Decreased in acute hepatitis. Cholesterol esters may be decreased also in chronic hepatitis and chronic biliary obstruction; in these situations the decrease in cholesterol ester exceeds the decrease in total cholesterol, which results in an ester/total cholesterol ratio of less than 65%.

**D. Method** Free cholesterol is precipitated with digitonin to produce digitonide, which is insoluble in petroleum ether. The normally occurring esters are extracted with petroleum ether and subsequently measured by the Liebermann-Burchard reaction (see Cholesterol, above).

**Creatine, Urine (24 Hours).** (Normal: See table.)

Urine Creatine & Creatinine, Normal Values (24 Hours)

	Creatine	Creatinine
Newborn	4.5 mg./Kg.	10 mg./Kg.
1-7 months	8.1 mg./Kg.	12.8 mg./Kg.
2-3 years	7.9 mg./Kg.	12.1 mg./Kg.
4-4½ years	4.5 mg./Kg.	14.6 mg./Kg.
9-9½ years	2.5 mg./Kg.	18.1 mg./Kg.
11-14 years	2.7 mg./Kg.	20.1 mg./Kg.
Adult male	0-50 mg.	25 mg./Kg.
Adult female	0-100 mg.	21 mg./Kg.

**A. Precautions** Collection of the 24-hour specimen must be accurate. The specimen may be refrigerated or preserved with 10 ml. of toluene or 10 ml. of 5% thymol in chloroform.

**B. Physiologic Basis** Creatine is an important constituent of muscle, brain, and blood, in the form of creatine phosphate it serves as a source of high-energy phosphate. Normally, small amounts of creatine are excreted in the urine, but in states of elevated catabolism and in the presence of muscular dystrophies, the rate of excretion is increased.

#### C. Interpretation

1. Elevated in muscular dystrophies such as progressive muscular dystrophy, myotonia atrophica, and myasthenia gravis, muscle wasting, as in acute poliomyelitis, amyotrophic lateral sclerosis, and myositis manifested by muscle wasting; starvation and cachectic states, hyperthyroidism, and febrile diseases.

2. Decreased in hypothyroidism, myotonia congenita, and renal insufficiency.

**D. Method** Creatine is determined indirectly by creatinine analysis. Creatine equals total creatinine minus preformed creatinine. Creatinine concentration is determined in an aliquot of the 24-hour urine specimen by the usual alkaline picrate method (preformed creatinine). A second aliquot is heated after

addition of acid to convert creatine to creatinine. The creatinine content of the heat- and acid-treated aliquot is then determined (total creatinine) and the 24-hour values are calculated.

**Creatinine, Plasma or Serum.** (Normal 0.8-2 mg./100 ml.)

**A. Precautions** Other materials than creatinine may react to give falsely high results.

**B. Physiologic Basis** Creatinine, which is derived from creatine, is excreted by filtration through the glomeruli of the kidney. Endogenous creatinine is apparently not excreted by renal tubules. Retention of creatinine is thus an index of glomerular insufficiency. Creatinine clearance closely approximates the inulin clearance and is an acceptable measure of filtration rate.

**C. Interpretation** Creatinine is elevated in acute or chronic renal insufficiency and urinary tract obstruction. Values of less than 0.8 mg./100 ml. are of no known significance.

**D. Method** In the Jaffé reaction, creatinine reacts with alkaline picrate solution to produce a yellow to red tautomer of creatinine picrate.

**Creatinine, Urine.**

See table for normal values.

**Enzymes, Serum.** See Amylase, Phosphatase, Transaminases.

**Globulin, Serum.** See Proteins, below.

**Glucose, Whole Blood, Plasma, Serum.**  
[Normal Fasting blood glucose (Folin), 80-120 mg./100 ml. Fasting blood glucose (true), 60-100 mg./100 ml.]

**A. Precautions** If determination is delayed beyond 1 hour, sodium fluoride, about 3 mg./ml. blood, should be added to the specimen. The filtrates may be refrigerated for up to 24 hours. Errors in interpretation may occur if the patient has eaten sugar or received glucose solution parenterally just prior to the collection of what is thought to be a "fasting" specimen. Whole blood, plasma, or serum may be used.

**B. Physiologic Basis.** The glucose concentration in extracellular fluid is normally closely regulated, with the result that a source of energy is available to tissues and no glucose is excreted in the urine. Hyperglycemia

and hypoglycemia are nonspecific signs of abnormal glucose metabolism

### C Interpretation

1 Elevated in diabetes mellitus hyperthyroidism adrenocortical hyperactivity (cortical excess) hyperpituitarism and hepatic disease (occasionally)

2 Decreased in hyperinsulinism adrenal insufficiency hypopituitarism hepatic insufficiency (occasionally) and functional hypoglycemia

### D Method

1 A protein-free blood filtrate is heated with alkaline cupric solutions. The cuprous oxide thus produced reduces phosphomolybdic acid to yield a blue color

2 A second method employs glucose oxidase which reacts specifically with glucose and does not measure other reducing substances

**Iodine** Protein bound (PBI), Butanol Extractable (BEI) Organic Serum. (Normal PBI 4-8 mcg /100 ml BEI 4-7 mcg /100 ml)

A Precautions Avoid iodine contamination of glassware and the use of iodine on the skin prior to venipuncture. The patient need not be fasting

B Physiologic Basis Thyroid hormone is normally the only organic iodine compound present in blood in significant concentration. The protein bound iodine is therefore a measure of circulating thyroxine

### C Interpretation

1 Elevated in hyperthyroidism thyroditis (during active stage) and pregnancy. Factitiously high levels may result from (1) administration of large doses of thyroid hormone (desiccated thyroid thyroxine) (2) ingestion of organic iodides and (3) administration of organic iodides used in x-ray diagnostic tests (cholecystograms urograms myelograms bronchograms uterosalpingograms). These diagnostic compounds may produce elevated iodine levels for one year or more

2 Reduced in hypothyroidism after use of mercurial diuretics (effect is only of few days duration) during administration of reserpine or during administration of triiodothyronine which suppresses thyroxine production by the thyroid gland

D Method Organic iodine is separated from inorganic iodide. The iodine is converted to inorganic form by ashing. Iodide thus released is determined by its catalytic effect

on the rate of reduction of ceric ion to cerous ion in the presence of arsenite

**Iron Serum** (Normal 75-175 mcg /100 ml)

A Precautions Hemolysis of blood must be avoided. The serum must be free of hemoglobin

B Physiologic Basis Iron concentration in the plasma is determined by several factors including absorption from the intestine storage in intestine liver spleen and marrow breakdown or loss of hemoglobin and synthesis of new hemoglobin

### C Interpretation

1 Elevated in hemochromatosis hemosiderosis (multiple transfusions excess iron administration hemolytic disease)

2 Reduced in iron deficiency anemias (nutritional chronic blood loss)

D Method Serum proteins are removed by precipitation with reagents which free the iron from the globulin to which it is bound. The iron may then be determined colorimetrically with a variety of reagents. Phenanthroline derivatives especially bathophenanthroline are particularly useful in determining the small concentrations present

**Iron-binding Capacity Serum** (Normal Total 300-360 mcg /100 ml Unsaturated 150-300 mcg /100 ml)

A Precautions None

B Physiologic Basis Iron is transported as a complex of the metal binding globulin transferrin or siderophilin. Normally this transport protein carries an amount of iron which represents about 30-40% of its capacity to combine with iron. Thus the 'unsaturated' iron binding capacity is normally 60-70% of the total capacity

C Interpretation of Unsaturated Iron Binding Capacity

1 Elevated in the presence of low serum iron or iron deficiency anemia

2 Decreased in the presence of high serum iron hemochromatosis hemosiderosis and hemolytic disease

D Method Iron as ferric ion or as ferric ammonium citrate is added to serum to saturate the transferrin (siderophilin) present. Excess free iron is removed on an ion exchange resin and total bound iron determined as above

Iron binding capacity equals total bound iron minus serum iron

**Lipase, Serum.** (Normal 0.2-1.5 units.)

**A. Precautions** None. The specimen may be refrigerated up to 24 hours prior to the determination.

**B. Physiologic Basis** A low concentration of fat splitting enzyme is present in circulating blood. In the presence of pancreatitis, pancreatic lipase is released into the circulation in higher concentrations which persist, as a rule, for a longer period than does the elevated concentration of amylase.

**C. Interpretation** Serum lipase is elevated in acute or exacerbated pancreatitis and in obstruction of pancreatic ducts by stone or neoplasm.

**D. Method** Serum is incubated with an olive oil emulsion at pH 7.0. The fatty acid released is titrated with 0.05-N NaOH. One unit equals 1 ml. 0.05-N fatty acid released per ml. of serum used.

**Magnesium, Serum.** (Normal 1.5-2.5 mEq./L.)

**A. Precautions** None.

**B. Physiologic Basis** Magnesium is primarily an intracellular electrolyte. In extracellular fluid it affects neuromuscular irritability and response. Magnesium deficit may exist with little or no change in extracellular fluid concentrations. Low magnesium levels in plasma have been associated with tetany, weakness, disorientation, and somnolence.

**C. Interpretation**

1. Elevated in renal insufficiency and in overtreatment with magnesium salts I.V. or I.M.

2. Reduced in chronic diarrhea, acute loss of enteric fluids, starvation, chronic alcoholism, chronic hepatitis, and hepatic insufficiency.

**D. Method**

1. Magnesium is precipitated as the phosphate and the phosphate determined by a colorimetric method (see Phosphorus, below).

2. An alternate colorimetric method utilizes titan yellow, which reacts with magnesium.

3. Newly developed methods utilize the chelating agent, ethylenediamine tetraacetic acid (EDTA) which removes  $Mg^{++}$  from solution to produce a change of color of an indicator dye.

**Nonprotein Nitrogen (NPN), Blood, Plasma, or Serum.** (Normal 15-35 mg./100 ml.)

**A. Precautions** See Urea, below.

**B. Physiologic Basis and Interpretation** See Urea below, and Creatinine above.

**C. Method** After removal of protein, nonprotein nitrogen is determined by acid hydrolysis of nitrogen-containing materials. Ammonia released is measured titrimetrically or colorimetrically.

**Phosphatase, Acid, Serum.** (Normal

Bodansky units, 0.5-2, King-Armstrong, 1-5, Gutman 0.5-2, Shinowara, 0-1.1, Bessey-Lowry, 0.1-0.63.)

**A. Precautions** Avoid hemolysis of the specimen, which releases erythrocyte phosphatase to give factitiously high results. Serum may be refrigerated 24-48 hours prior to determination.

**B. Physiologic Basis** Phosphatase active at pH 4.9 is present in high concentrations in the prostate gland and in erythrocytes. In the presence of carcinoma of the prostate which has gone beyond the capsule of the gland or has metastasized serum acid phosphatase concentration is increased.

**C. Interpretation** Increased in carcinoma of the prostate metastatic or invasive beyond the capsule of the gland, and occasionally in acute myelocytic leukemia.

**D. Method** See Alkaline Phosphatase, below. pH should be maintained at 4.9.

**Phosphatase, Alkaline, Serum.** (Normal

Bodansky, 2-5 units, King-Armstrong 5-13 Gutman, 3-10 Shinowara, 2.2-8.6, Bessey-Lowry, children 2.8-6.7, Bessey-Lowry, adults, 0.8-2.3.)

**A. Precautions** Serum may be kept in refrigerator 24-48 hours, but values may increase slightly (10%). The specimen will deteriorate if not refrigerated.

**B. Physiologic Basis** Alkaline phosphatase is present in high concentrations in growing bone and in bile. Concentration in circulating blood reflects phosphatase activity in bone growth and repair. If hepatic excretory ducts become occluded phosphatase concentration in the blood increases.

**C. Interpretation**

1. Elevated in -

(1) Children (normal growth of bone).

(2) Osteoblastic bone disease Hyperparathyroidism rickets and osteomalacia neoplastic bone disease (osteosarcoma metastatic neoplasms multiple myeloma) ossification as in myositis ossificans Paget's disease (osteitis deformans) and Boeck's sarcoid

(3) Hepatic duct or cholangiolar obstruction due to stone stricture or neoplasm

(4) Hepatic disease resulting from drugs such as chlorpromazine methyltestosterone

2 Decreased in hypothyroidism and in growth retardation in children

**D Method** A suitable phosphate ester (glyceryl phenyl *p* nitrophenyl) is employed as a substrate for alkaline phosphatase action. The pH is maintained at 8.6 to 10.4 varying with the method. Either the phosphate or the organic moiety of the ester released by enzyme activity is measured and reported in units related to phosphate released.

**Phosphorus Inorganic Serum (Normal)**  
Children 4-7 mg/100 ml Adults  
3-4.5 mg/100 ml or 0.9-1.5 mM/L

**A Precautions** Glassware cleaned with phosphate cleaners must be thoroughly rinsed. The fasting state is necessary to avoid postprandial depression of phosphate associated with glucose transport and metabolism.

**B Physiologic Basis** The concentration of inorganic phosphate in circulating plasma is influenced by parathyroid gland function in testinal absorption renal function bone metabolism and nutrition.

#### C Interpretation

1 Increased in renal insufficiency hypoparathyroidism and hypervitaminosis D

2 Decreased in hyperparathyroidism hypovitaminosis D (rickets osteomalacia) malabsorption syndrome (steatorrhea) some forms of renal tubular insufficiency postprandial state and after insulin

**D Method** After removal of serum protein with trichloroacetic acid phosphomolybdic acid is produced by the reaction of phosphorus with molybdic acid. Molybdate is reduced by one of several compounds (stannous chloride para aminonaphthyl sulfonic acid elon) to produce a blue color the intensity of which is proportionate to the amount of phosphorus present.

**Potassium Serum or Plasma (Normal)**  
3.5-5 mEq/L 14-20 mg/100 ml

**A Precautions** Avoid hemolysis which releases erythrocyte potassium. Serum must be separated promptly from the clot or plasma from the red cell mass to prevent diffusion of potassium out of erythrocytes.

**B Physiologic Basis** Potassium concentration in plasma determines the state of neuromuscular and muscular irritability. Elevated or decreased concentrations of potassium impair the capability of muscle to contract.

#### C Interpretation

1 Increased in renal insufficiency especially in the presence of increased rate of protein or tissue breakdown, adrenal insufficiency and too rapid administration of potassium salts especially I.V. and with spironolactone (Aldactone®) administration.

2 Decreased in

(1) Inadequate intake (starvation)

(2) Inadequate absorption or unusual enteric losses Vomiting diarrhea or malabsorption syndrome

(3) Unusual renal loss Secondary to hyperadrenocorticism (especially hyperaldosteronism) and to adrenocorticosteroid therapy metabolic alkalosis use of diuretics such as chlorothalidate and its derivatives and the mercurials and renal tubular defects such as the De Toni Fanconi syndrome and renal tubular acidosis.

(4) Abnormal redistribution between extracellular and intracellular fluids Familial periodic paralysis testosterone administration

**D Method** Determination by flame photometry has almost completely displaced colorimetric and titrimetric methods.

**Proteins Serum or Plasma (Includes Fibrinogen) (Normal See Interpretation below)**

**A Precautions** Serum or plasma must be free of hemolysis. Since fibrinogen is removed in the process of coagulation of the blood fibrinogen determinations cannot be done on serum.

**B Physiologic Basis** Concentration of protein determines colloidal osmotic pressure of plasma. The concentration of protein in plasma is influenced by the nutritional state hepatic function renal function occurrence of disease such as multiple myeloma and metabolic errors. Variations in the several fractions of plasma proteins may signify the presence of specific disease.



## C. Interpretation

1. Total protein, serum (normal 6-8 Gm./100 ml.) - See albumin and globulin fractions, below.

2. Albumin, serum or plasma (normal 3.5-5 Gm./100 ml.) - See Method, below.

(1) Elevated in dehydration, shock, hemoconcentration, administration of large quantities of concentrated albumin "solution" I.V.

(2) Decreased in malnutrition, malabsorption syndrome, acute or chronic glomerulonephritis, nephrosis, acute or chronic hepatic insufficiency, neoplastic diseases, and leukemia.

3. Globulin, serum or plasma (normal 1.5-3 Gm./100 ml.) - See Method, below.

(1) Elevated in hepatic disease, infectious hepatitis, cirrhosis of the liver, biliary cirrhosis, and hemochromatosis, disseminated lupus erythematosus, acute or chronic infectious diseases, particularly lymphopathia venereum, typhus fever, leishmaniasis, schistosomiasis, and malaria, multiple myeloma, and Boeck's sarcoid.

(2) Decreased in malnutrition, congenital agammaglobulinemia, acquired hypogammaglobulinemia, and lymphatic leukemia.

4. Fibrinogen, plasma (normal 0.2-0.6 Gm./100 ml.) -

(1) Elevated in glomerulonephritis, nephrosis (occasionally), and infectious diseases.

(2) Decreased in accidents of pregnancy (placental ablation, amniotic fluid embolism, violent labor), acute and chronic hepatic insufficiency, and congenital fibrinogenopenia, and occasionally with prostatic carcinoma.

## D. Method

1. Digestion of protein by the Kjeldahl method or modifications thereof is followed by measurement of nitrogen released as ammonia. Other methods rely on formation of copper-protein complexes which can be measured colorimetrically.

2. The fractions of serum or plasma proteins can be measured after separation by salting out with appropriate concentration of sodium sulfate or sodium sulfite. Electrophoresis (free or paper methods) provides a suitably accurate separation of protein fractions for clinical diagnostic purposes.

Sodium, Serum or Plasma. (Normal 136-145 mEq./L.)

A. Precautions Glassware must be completely clean.

B. Physiologic Basis Sodium constitutes 140 of the 155 mEq. of cation in plasma.

With its associated anions it provides the bulk of osmotically active solute in the plasma, thus affecting the distribution of body water significantly. A shift of sodium into cells or a loss of sodium from the body results in a decrease of extracellular fluid volume with consequent effect on circulation, renal function, and nervous system function.

## C. Interpretation

1. Increased in dehydration (water deficit), CNS trauma or disease, and hyperadrenocorticism due to hyperaldosteronism or to corticosterone or corticoid excess.

2. Decreased in adrenal insufficiency, renal insufficiency, especially with inadequate sodium intake, renal tubular acidosis, as a physiologic response to trauma or burns (sodium shift into cells), unusual losses via the gastrointestinal tract, as in acute or chronic diarrhea, intestinal obstruction or fistula, and in unusual sweating with inadequate sodium replacement. In some patients with edema associated with cardiac or renal disease, serum sodium concentration is low even though total body sodium content is greater than normal, water retention and abnormal distribution of sodium between intracellular and extracellular fluid contribute to this paradoxical situation. Hyperglycemia occasionally results in shift of intracellular water to the extracellular space, producing a dilutional hyponatremia.

D. Method Determination by flame photometry has largely replaced colorimetric and gravimetric methods.

Transaminase & Allied Enzyme Tests, Serum or Serous Fluid [Normal Glutamic oxaloacetic transaminase (SGOT) 5-40 units. Glutamic pyruvic transaminase (SGPT) 5-35 units. Lactic dehydrogenase (LDH) 200-680 units.]

A. Precautions None.

B. Physiologic Basis Glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and lactic dehydrogenase are all intracellular enzymes involved in amino acid or carbohydrate metabolism. The enzymes are present in high concentrations in muscle, liver, and brain. Elevations of concentrations of these enzymes in the blood indicate necrosis or disease, especially of these tissues.

C. Interpretation Elevated in myocardial infarction, acute infections or toxic hepatitis, cirrhosis of the liver, liver neoplasm, metastatic or primary, and in transudates associ-

ated with neoplastic involvement of serous cavities. SGOT is elevated in muscular dystrophy, dermatomyositis, and paroxysmal myoglobinuria.

**D Method** Reduction of diphosphopyridine nucleotide (DPN) in the presence of an appropriate substrate is a measure of enzyme activity. This can be measured by changes in optical density of the solution in which the reaction occurs. Other methods employ colorimetric reactions which measure products of enzyme action on suitable substrates.

**Urea & Urea Nitrogen, Blood, Plasma, or Serum.** (Normal BUN 10-20 mg./100 ml.)

**A Precautions** Do not use ammonium oxalate or "double oxalate" as anticoagulant for the ammonia will be measured as urea (see Method). Do not use too much oxalate, for it will impair urease activity.

**B. Physiologic Basis** Urea, an end-product of protein metabolism, is excreted by the kidney. In the glomerular filtrate the urea concentration is the same as in the plasma. Tubular reabsorption of urea varies inversely with rate of urine flow. Thus urea is a less useful measure of glomerular filtration than is creatinine, which is not reabsorbed. BUN varies directly with protein intake and inversely with the rate of excretion of urea.

### C. Interpretation

#### 1. Elevated in -

(1) Renal insufficiency - Nephritis, acute and chronic, acute renal failure (tubular necrosis) urinary tract obstruction.

(2) Increased nitrogen metabolism associated with diminished renal blood flow or impaired renal function - Dehydration from any cause, gastrointestinal bleeding (combination of increased protein absorption from digestion of blood, plus decreased renal blood flow).

(3) Decreased renal blood flow - Shock, adrenal insufficiency, occasionally congestive heart failure.

2. Decreased in hepatic failure, nephrosis not complicated by renal insufficiency, and cachexia.

**D. Method** Urease is employed to hydrolyze urea to ammonium carbonate. The ammonia is measured titrimetrically or colorimetrically.

**Uric Acid, Serum or Plasma.** (Normal 3-6 mg./100 ml.)

**A. Precautions:** If plasma is used, lithium oxalate should be used as the anticoagulant, potassium oxalate may interfere with the determination.

**B Physiologic Basis** Uric acid, an end-product of nucleoprotein metabolism, is excreted by the kidney. Gout, a genetically transmitted metabolic error, is characterized by an increased plasma or serum uric acid concentration, an increase in total body uric acid, and deposition of uric acid in tissues. An increase in uric acid concentration in plasma and serum may accompany increased nucleoprotein catabolism (blood dyscrasias, therapy with anti-leukemic drugs), or decreased renal excretion.

### C. Interpretation

1. Elevated in gout, toxemia of pregnancy (eclampsia), leukemia, polycythemia, therapy with anti-leukemic agents, and renal insufficiency.

2. Decreased in acute hepatitis (occasionally).

**D. Method** Uric acid reduces phosphotungstate and cyanide to yield a blue color. An alternative and more specific method employs uricase which destroys uric acid. The decrease in optical density of the specimen following incubation with uricase is a measure of uric acid concentration.

## PHYSICAL MANAGEMENT OF THE HEMIPLEGIC

Advances in physical medicine have given new hope to the patient who suffers from hemiplegia, a condition which is encountered more and more in clinical medicine. The following program is intended to serve only as a guide, it applies to the typical case of cerebral vascular accident, but the principles are the same in hemiplegia due to any cause.

### Bed Phase.

The bed phase starts on the second or third day of the illness or as soon as the patient is conscious. The patient's bed should be of chair height and should have side rails and an overhead trapeze.

**A. Exercises** Start with 10 minutes of exercise every 2 hours and increase to 30 minutes of exercise every 2 hours.

1. With the uninvolved arm and leg turn from the back to the side to the abdomen, then to the other side and then back. Repeat in the opposite direction.

2. With the uninvolved hand on the trapeze, pull to a sitting position and back.

3. Move sideways, upward, and downward in bed.

4. Sit up on the edge of the bed with the side rail removed, legs dangling, and move along the edge of the bed with the aid of the good arm and leg.

**B Self Care** (All done with the uninvolved hand.)

1. Toilet activities - Wash face and hands, comb hair, shave.

2. Feeding activities - At first in bed with the back rolled up, later, sitting on the edge of the bed.

**C. Bracing** None during the bed phase

### Standing Phase.

This phase starts 3-5 days after the beginning of the bed phase, and replaces the bed phase as soon as possible. The patient is placed in an armchair with his unaffected side next to the foot of the bed, the vertical bar of the overhead frame in reach of his uninvolved hand and the paralyzed arm in a sling

**A. Exercise** Start with 10 minutes of exercise every 2 hours and increase to 30 minutes every 2 hours.

1. Rise to a standing position on the uninvolved leg. Sit back.

2. Standing with the uninvolved hand on the vertical bar of the overhead frame,

perform a slight knee bend and straighten up. Repeat with gradually deeper knee bends.

3. Stand with the uninvolved hand on the vertical bar of the bed frame. Go up on toes, come back down

**B Self Care** (Using the uninvolved hand.)

1. Toilet activities - Complete bath in bed.

2. Dressing activities - Dress and undress except for shoes.

**C. Bracing**

1. A flat wooden splint (attached to the volar surface with elastic bandage or straps) is applied from one inch below the elbow to  $\frac{1}{2}$  inch beyond the fingertips of the paralyzed arm.

2. Keep the paralyzed arm in a sling to prevent pull on shoulder.

3. If after 2 weeks the paralyzed leg remains completely flail, a long-leg brace is needed in order to continue rehabilitation.

### Stair-climbing Phase

This phase starts 2-10 days after the beginning of the standing phase, and should replace the standing phase as soon as possible.

**A. Exercises** These are performed 4 times a day, increasing from several steps to a whole flight of stairs. The patient is placed in a chair facing the foot of a flight of stairs, his uninvolved arm next to the banister. The paralyzed arm is splinted and in a sling, and the paralyzed leg is in a long-leg brace if necessary.

1. Pull to a standing position, holding to the banister with the uninvolved hand, step up one step with the uninvolved leg, and then pull the paralyzed leg up to the same step. Continue for several steps.

2. Step backward and down with the paralyzed leg and put the uninvolved leg down next to it. Continue for several steps.

3. While several stairs up, turn toward and reach over to the opposite banister. Step forward and down with the paralyzed leg. Then place the uninvolved leg next to the paralyzed leg and continue.

**B Self Care** Complete toilet and feeding and dressing activities should be possible by this time.

**C. Bracing**

1. A long-leg brace should be worn (see Standing Phase).

2. If the patient has a foot drop during stair climbing, he should wear a short-leg brace with a 90° posterior stop at the ankle.

3. If the patient shows evidence of inversion or eversion of the foot, he should have a short-leg brace with a T-strap.

4. If function has returned to the paralyzed hand, the splint may be discarded. Otherwise it should be worn intermittently.

#### Cane-walking Phase.

This phase starts as soon as the patient is able to walk up and down a whole flight of stairs without tiring. The paralyzed arm is kept in a sling and a cane is held with the uninvolved hand. Two different cane-walking gaits are recommended for the hemiplegic patient.

**A Slow Gait** (For fearful patients or patients with poor balance) Move the cane forward, place the uninvolved foot next to the cane, and then drag the paralyzed foot next to it

**B Fast Gait** Standing on the uninvolved leg move the cane and the paralyzed leg forward simultaneously and put weight on them. Swing the uninvolved leg through in front of the cane and the paralyzed leg and put weight on it. Continue in this fashion

#### Special Problems in Hemiplegic Patients

##### A Care of the Paralyzed Upper Extremity

1. Complete absence of function - In most cases no useful function returns to the paralyzed upper extremity, and the wrist and hand are best supported in the splint. The sling may be discarded later, when the shoulder muscles become spastic and the patient feels limited by the sling. With his uninvolved hand, the patient should move the paralyzed fingers, wrist, and elbow through the full range of motion twice a day. In order to move the paralyzed shoulder through the full range of motion the patient may need a cord through an overhead pulley by means of which the paralyzed arm (tied at the wrist) can be pulled up as high as possible with the uninvolved arm

2. Partial function - If only partial function returns to the paralyzed extremity, the patient should use it only to the extent to which it is helpful or expedient. For other activities the patient should be trained in the use of the good extremity.

3. Complete function - If complete function returns, the patient should use the extremity as much as possible.

**B. Treatment of Aphasia** If aphasia occurs speech therapy (daily in half-hour periods) should be started as soon as possible. If sensory or receptive aphasia is present, the above program may be rendered extremely difficult since it is based on the ability of the patient to understand what is required of him.

**C Care of Hemianopsia** (A minor problem) If hemianopsia is present, the patient should be trained to turn his head to the hemianopsic side in order to bring his visual field in front of him. Later some adjustment in the visual field occurs.

**D Care of Sphincters** Some hemiplegics are incontinent in the early phase. An indwelling catheter is rarely necessary. The patient should be reminded to empty his bladder voluntarily at hourly intervals. These intervals can be gradually increased.

**E Organic Mental Syndrome** When mentation is impaired the entire rehabilitation program becomes difficult. The patient may either not understand or may be unable to concentrate. The confusion may be present at one time and absent at another, and advantage should be taken of the patient's lucid periods. The organic mental syndrome occurs usually in patients who have had several strokes. The patient's mental state usually improves considerably during an active rehabilitation program.

## ABBREVIATIONS

A, artery	EMG, electromyography
Å, angstrom	ESR, erythrocyte sedimentation rate
āā, of each	FF, filtration fraction
A <sub>2</sub> , aortic second sound	FSH, follicle-stimulating hormone
ABE, acute bacterial endocarditis	GFR, glomerular filtration rate
a.c., before meals	Hct., hematocrit
ACD, anterior chest diameter	Hgb., hemoglobin
ACTH, adrenocorticotrophic hormone	ICS, intercostal space
APC, acetylsalicylic acid, phenacetin, and caffeine	ICW, intracellular water
ASA, acetylsalicylic acid	I.M., intramuscular
ASO, arteriosclerosis obliterans	INH, isonicotinic acid hydrazide
AsCAD, arteriosclerotic coronary artery disease	IPPB, intermittent positive pressure breathing
BAL, British anti-Lewisite	I.Q., intelligence quotient
BBB, bundle branch block	ISW, interstitial water
BBT, basal body temperature	I.U., international unit
BCG, bacille Calmette-Guerin	I.V., intravenous
b.i.d., twice a day	KP, keratitic precipitates
BLB, Boothby-Lovelsce-Bulbulian (oxygen mask)	KW, Keith-Wagener ( <i>ophthalmoscopic findings</i> )
BMR, basal metabolic rate	LA, left atrium
BUN, blood urea nitrogen	LBBC, left bundle branch block
Cal., Calorie ( <i>i.e.</i> , large calorie, or 1000 calories)	LDH, lactic acid dehydrogenase
CBC, complete blood count	LE, lupus erythematosus
C-F, complement fixation test	LMP, last menstrual period
CHO, carbohydrate	LVH, left ventricular hypertrophy
CNS, central nervous system	M, molar
CSF, cerebrospinal fluid	M1, mitral first sound
D and C, dilatation and curettage	MAC, maximum allowable concentration
DDS, diaminodiphenylsulfone	mcg., microgram
DDT, diphenylthiourea	MCH, mean corpuscular hemoglobin
DPT, diphtheria-pertussis-tetanus	MCHC, mean corpuscular hemoglobin concentration
ECG, electrocardiogram, electrocardiography	MCV, mean corpuscular volume
ECW, extracellular water	MCL, midcostal line
EDTA, calcium disodium edathamil	mEq., milliequivalent
EEG, electroencephalogram, electroencephalography.	MLD, minimum lethal dose
EFA, essential fatty acids	mM., millimols
Eq., equivalent	mOsm., milliosmols
	mrem, 1/1000 rem
	NPN, nonprotein nitrogen
	OT, old tuberculin
	PA, posteroanterior

PAM, penicillin with aluminum monostearate in oil  
 PAS, para-aminosalicylic acid  
 PBI, protein-bound iodine  
 p c , after meals  
 pCO<sub>2</sub>, carbon dioxide partial pressure  
 PCV, packed cell volume  
 pH, hydrogen ion concentration  
 PID, pelvic inflammatory disease  
 PIE, pulmonary infiltration with eosinophils  
 pK, dissociation constant  
 PMI, point of maximal impulse  
 PMN, polymorphonuclear neutrophil  
 PMP, past menstrual period  
 PPD, purified protein derivative  
 p p m , parts per million  
 p r n , as needed  
 PZA, pyrazinamide  
 q s ad, to a sufficient quantity  
 q i.d , four times daily  
 r, roentgen  
 RA, right atrium  
 rad, an energy transfer of 100 ergs/Gm. of irradiated object

RBBB, right bundle branch block  
 RBC, red blood count  
 RPF, renal plasma flow  
 RV, right ventricle  
 RVH, right ventricular hypertrophy  
 SBE, subacute bacterial endocarditis  
 SGOT, serum glutamic oxaloacetic transaminase  
 SGPT, serum glutamic pyruvic transaminase  
 stat , immediately  
 STS, serologic tests for syphilis  
 TAO, thromboangiitis obliterans  
 TBW, total body water  
 TCID<sub>50</sub>, 1/50 of the tissue culture immunizing dose  
 TIBC, total iron-binding capacity  
 t i d , 3 times daily  
 TPI, Treponema pallidum immobilization  
 V, vein  
 vol , volume  
 Vol %, volumes per cent  
 VC, vena cava  
 WBC, white blood count

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